frontiers | Research Topics

Women in science - regulatory science 2021

Edited by
Mette Due Theilade Thomsen and Lisbeth Ehlert Knudsen

Published in
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-83252-059-8
DOI 10.3389/978-2-83252-059-8

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Women in science - regulatory science 2021

Topic editors

Mette Due Theilade Thomsen — PIP Adviser, Denmark

Lisbeth Ehlert Knudsen — University of Copenhagen, Denmark

Citation

Thomsen, M. D. T., Knudsen, L. E., eds. (2023). *Women in science - regulatory science 2021*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83252-059-8

Table of contents

frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 16 March 2023
DOI 10.3389/fmed.2023.1159815

OPEN ACCESS

EDITED AND REVIEWED BY
Christine Gispen-de Wied,
Gispen4RegulatoryScience, Netherlands

*CORRESPONDENCE
Mette Due Theilade Thomsen
✉ mt@pipadviser.com
Lisbeth Ehlert Knudsen
✉ liek@sund.ku.dk

SPECIALTY SECTION
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

RECEIVED 06 February 2023
ACCEPTED 03 March 2023
PUBLISHED 16 March 2023

CITATION
Thomsen MDT and Knudsen LE (2023) Editorial: Women in science—Regulatory science 2021. *Front. Med.* 10:1159815. doi: 10.3389/fmed.2023.1159815

Editorial: Women in science—Regulatory science 2021

Mette Due Theilade Thomsen[1]* and Lisbeth Ehlert Knudsen[2]*

[1]PIP Adviser, Lyngby, Denmark, [2]Department of Public Health, University of Copenhagen, Copenhagen, Denmark

KEYWORDS

scientific advice, drug repurposing, pediatric drug development, drug registration, healthcare, funding, clinical research, gender research

Editorial on the Research Topic
Women in science—Regulatory science 2021

Introduction

All publications in this Research Topic on Women in Regulatory Science have female first authors, and the diversity in scientific subjects and high quality of the publications truly underline that regulatory science is blessed with a high number of very specialized, extremely skillful and high performing women. The publications indeed demonstrate how women are moving science forward.

Scientific advice

Murphy et al. examine the contributions of patient participation in scientific advice procedures at the European Medicines Agency (EMA), describing methodology used to involve patients in scientific advice and presenting an analysis of feedback received from EMA procedure coordinators as well as patients who have participated. There is a significant added value from patient engagement in EMAs Scientific Advice procedures suggesting the need to further expand patient input to real-world evidence for the benefit of public health.

Dekker et al. address new approaches in the use of remote monitoring technologies (RMT) in clinical registration trials by evaluating regulatory qualification opinions, qualification and scientific advices provided between 2013 and 2019 by the EMA Committee for Medicinal Products for Human Use (CHMP). The RMTs included accelerometers to measure activity and/or sleep, mobile applications and glucose monitoring devices, mostly proposed as secondary or exploratory endpoints. CHMP recommendations concerned relevance, validation, precision, compliance and actual use as well as privacy and data handling. RMTs in registration trials are still rare but use has increased over time. This insight may stimulate the use of novel RMTs in a regulatory context.

Repurposing of medicines

Drug repurposing is the process of identifying a new use for an existing medicine in an indication outside the scope of the original approved indication. Asker-Hagelberg et al. address the issue of repurposing of authorized medicines taking the examples collected

during the COVID-19 pandemic into consideration and stressing the need for initiatives. A European Union framework for repurposing of established medicines is described.

Pediatric drug development

The EU Pediatric Regulation was introduced in 2007 and is currently undergoing revision. A pediatric legislation has existed for even longer in the USA. Existing differences in the legislative framework may cause different pediatric requirements for similar indications granted for similar drugs across jurisdictions. In a cross-sectional study, Christiansen et al. study mandatory requirements for pediatric drug development in the EU and the US, comparing requirements for therapeutic indications granted at the time of initial approval for novel drugs approved in the two regions from 2010 to 2018. This is an important contribution to the evaluation of how aligned requirements for pediatric drug development are across the regions.

Global drug registration requirements

Zhong et al. compared registration requirements to Proprietary Chinese medicine in Hong Kong and Canada based on publicly available information. Similarities and differences exist between the two regulatory systems in terms of quality, safety and efficacy requirements. Knowledge of the Proprietary Chinese Medicines product license application procedure and requirements in Hong Kong and Canada will enable an appropriate strategy for gaining product approval.

General healthcare

Enticott et al. describe Australian experiences with a Learning Health System stressing the need for cross disciplinary work and data sharing. The study aimed to describe the process and present a perspective on a coproduced Learning Health System framework, with development led by publicly funded Academic Health Research Translation Centres with a mandate to integrate research into healthcare to deliver impact. This continuous learning approach aims to deliver evidence-based healthcare improvement.

Funding and innovation

Diabetes Mellitus (DM) is one of the World Health Organization's priority diseases under research by the program of Innovative Medicines Initiative (IMI). Brito et al. reviewed the Impact of the IMI initiatives related to DM by analyzing publications from projects under the initiative. The IMI funded projects identified new biomarkers, medical and research tools, clinical trial designs, clinical endpoints and therapeutic targets, to name a few. Based on the scientific data produced, the authors provide a joint vision with strategies for integrating personalized medicine into healthcare practice.

Janssens et al. studied patient preferences for Multiple Myeloma Treatments by qualitative interviews in 4 EU countries and thematic analysis. Results pointed at the need for Multiple Myeloma drug development, evaluation and individual treatment not only focusing on extending the life but also taking side effects into account as these significantly impact Multiple Myeloma patients' quality of life.

Sessa et al. describe the role and limitations of the European Patients Academy on Therapeutic Innovation (EUPATI) in Switzerland (CH) in promoting patient involvement in medicines research and development. EUPATI CH initiated a multi-stakeholder survey involving patient representatives, academia, pharmaceutical industry, healthcare professionals, and government agencies. A need for collaboration amongst stakeholders as well as funding, knowledge and human resources was identified.

Clinical development

Kearney et al. describe how various stakeholders can utilize regulatory affairs and clinical affairs to navigate the nuanced landscape behind the development and use of clinical diagnostic products. This work emphasizes the critical importance of utilizing regulatory affairs and clinical affairs as an integral part of product development to ensure sustained innovation.

Monti et al. stress the need for academic follow-up studies postmarketing identifying barriers and possible solutions from experiences with breast cancer. The authors describe the regulatory hurdles of getting approvals for an academic study funded by an EU call on validation of biomarkers for personalized cancer medicine.

We conclude this editorial with a gender-related research study. Gender medicine investigates the influence of sex/gender on the pathophysiology, prevention and treatment of disease, and on social and psychological aspects. Medical research was previously performed dominantly on men in preclinical and clinical studies, but the picture is changing. Artificial intelligence (AI) algorithms assist health professionals with data management, preclinical image-based diagnostics, robotic surgery, prediction models, and decision-making support. Yoon et al. conducted a bibliometric analysis of gender-related articles in medical AI over 20 years. The number of publications and percentage of gender-related articles in medical AI fields increased from 2001 to 2020, with a steep increase in the last 5 years. This underlines an increased focus on gender-related medical research, to the benefit of the patients.

Author contributions

All authors contributed to the article and approved the submitted version.

Conflict of interest

MT was employed by PIP Adviser.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

frontiers in Medicine

POLICY AND PRACTICE REVIEWS
published: 09 March 2021
doi: 10.3389/fmed.2021.617625

A Comparative Study for License Application Regulations on Proprietary Chinese Medicines in Hong Kong and Canada

Linda L. D. Zhong[1,2,3]*, *Wai Ching Lam*[1,2,4], *Fang Lu*[5], *Xu Dong Tang*[5], *Aiping Lyu*[1,2], *Zhaoxiang Bian*[1,2] *and Heather Boon*[3]*

[1] Hong Kong Chinese Medicine Clinical Study Centre, Hong Kong Baptist University, Hong Kong, China, [2] School of Chinese Medicine, Hong Kong Baptist University, Hong Kong, China, [3] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [4] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, United States, [5] China Academy of Chinese Medical Sciences, Beijing, China

OPEN ACCESS

Edited by:
Mette Due Theilade Thomsen,
PIP Adviser, Denmark

Reviewed by:
Lawrence Liberti,
Centre for Innovation in Regulatory Science, United Kingdom
Frits Lekkerkerker,
Consultant, Netherlands

***Correspondence:**
Linda L. D. Zhong
ldzhong0305@gmail.com
Heather Boon
heather.boon@utoronto.ca

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: 10 November 2020
Accepted: 03 February 2021
Published: 09 March 2021

Citation:
Zhong LLD, Lam WC, Lu F, Tang XD, Lyu A, Bian Z and Boon H (2021) A Comparative Study for License Application Regulations on Proprietary Chinese Medicines in Hong Kong and Canada. Front. Med. 8:617625. doi: 10.3389/fmed.2021.617625

Ethnopharmacological Relevance: Chinese Medicine plays a symbolic role among traditional medicines. As Chinese Medicine products are widely used around the globe, regulations for Chinese Medicine products are often used as models for the efficient regulation of natural products that are safe, and high-quality.

Aim of the Study: We aimed to compare the regulatory registration requirements for Proprietary Chinese Medicines in Hong Kong and Canada.

Materials and Methods: We compared registration requirements for Proprietary Chinese Medicine in Hong Kong and Canada based on publicly available information provided by the respective Regulators. A marketed product, Zhizhu Kuanzhong Capsule (SFDA approval number Z20020003; NPN approval number 80104354), was used as a case study to demonstrate the similarities and differences of the requirements in both Hong Kong and Canada.

Results: There were similarities and differences between the two regulatory systems in terms of the quality, safety and efficacy requirements. Despite the superficial appearance of similar categories and groups/classes, Hong Kong requires significantly more primary test data compared to Canada's reliance on attestation to manufacturing according the standards outlined in approved reference pharmacopeias/texts.

Conclusion: Improved understand of the similarity and differences will enable applicants to plan appropriate strategies for gaining product approval. Exploring ways to harmonize the regulatory process has the potential to benefit manufacturers, regulators, and patients by increasing efficiency and decreasing costs.

Keywords: proprietary Chinese medicine, traditional Chinese medicine, herbal medicine, natural health products, Chinese medicine regulation, Chinese medicine registration, product license application regulation, Zhizhu Kuanzhong

INTRODUCTION

Regulation of health products is generally considered necessary to protect the public. The vast majority of countries have implemented policies and practices aimed at reviewing the safety and effectiveness of health products before allowing them to be marketed to the general population. In an increasingly globalized marketplace, manufacturers face a wide array of regulatory regimes as each country requests different information or evidence and often requires different standards for assessing products. While recognizing the right of each sovereign nation to set its own standards, one wonders whether voluntary harmonization of key standards and evidence requirements might save significant time and money ultimately increasing access of populations to safe, effective and high quality products.

The implementation of evidence-based reviews to avoid costly replication of efforts and facilitate timely access to medications has been a topic of global discussion and debate. For example, in the United States, the *Prescription Drug User Fee Act VI* and *21st Century Cures Act* recommend a more effective and efficient regulatory review model, authorizing the Food and Drug Administration to enhance capacity to review products under a variety of models and pathways (1). In the European Union, the European Medicines Agency has been taking steps toward more flexible approaches to its drug approval system (2).

Traditional medicine is defined by the World Health Organization as "the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" (3). Traditional medicine products often have long histories of use in their original cultural settings but may have limited translational research supporting their use. As demand for these products increases around the world, especially in markets outside the country of origin, there is an urgent need for regulation of traditional medicines. This creates challenges for regulators and manufactures. Regulators look for conventional scientific evidence of safety and efficacy, while consumers and manufacturers are concerned that over regulation may limit patient access to safe and effective medicines that have been used for hundreds of years in their country of origin. Unlike Western biomedicine, health claims of traditional medicines are sometimes difficult to evaluate in jurisdictions outside the country of origin where there may be limited experience or expertise in assessing the quality of traditional products. In addition, the significant variation in guidelines and requirements for product registration/licensing creates unnecessary barriers for manufacturers.

In order to explore these challenges, we conducted a case study of the regulatory requirements for obtaining a product license for Zhizhu Kuanzhong Capsule, a Proprietary Chinese Medicine in two policy environments: Hong Kong and Canada. Hong Kong and Canada were chosen because they both have well-developed regulatory systems for traditional medicines, but are based in very different cultures which allows the identification of similarities and differences that may have relevance for a range of systems. We focused on the quality control, safety, and effectiveness aspects of the regulatory process as these are arguably more amenable to possible harmonization across states and cultures. The paper concludes with a discussion of components of the regulatory process where harmonization may have the greatest impact to facilitate the efficiency of the regulatory approval process while also enhancing its rigor and ability to achieve the objective of protecting the public.

Abbreviations: NHP, Natural Health Product; NNHPD, Natural and Non-prescription Health Products Directorate; NPN, (Canada) Natural Product Number; SFDA, (Mainland China and Hong Kong) State Food and Drug Administration; ZZKZ, Zhizhu Kuanzhong.

DEFINITION AND REGULATIONS

The regulatory pathway and requirements for Proprietary Chinese Medicine in Hong Kong and Canada are available online on their respective regulatory bodies' websites (4–7).

In Hong Kong, Proprietary Chinese Medicine is regulated by Chinese Medicine Council of Hong Kong, a statutory body established under the Chinese Medicine Ordinance established since 1999. Under the regulation, the selection of the classification category and the registration group of a Proprietary Chinese Medicine product license application is a decision made by the applicant and reviewed by the regulatory body. The registration requirements are dependent on the selected classification category and registration group (**Figure 1**). Other than the "New Medicine Category" that must be registered under Group III, for Proprietary Chinese Medicines under the "Established medicines category" (ancient or pharmacopeia prescriptions with original dose form) and "Non-established medicines category" (health-preserving medicines and single Chinese medicine granules), there are no distinctive guidelines which help the applicant to determine whether products should be registered under Group I, Group II or Group III. The applicants may choose to apply for registration in any of the three groups (8). This creates an incentive for applicants to select registration groups with fewer requirements, i.e., Group I with basic documents or Group II with further safety and quality supporting documents, instead of Group III which requires the submission of a dossier with comprehensive documents (see **Table 1** for a summary of required materials). Though the applicants are encouraged to consult the Chinese Medicine Regulatory Office of the Department of Health, currently there is no official pre-submission meeting arrangement in Hong Kong to help ensure that the applicants have selected the right product license registration group.

In Canada, Proprietary Chinese Medicine is defined as a natural health product (NHP) and regulated by Natural and Non-prescription Health Products Directorate of Health Canada under the Natural Health Products Regulations which came into effect on January 1, 2004. A wide range of health products whose active ingredients exist in nature and are used for self-limiting conditions fall within the category of natural health products including herbal medicines, vitamins and minerals, essential fatty

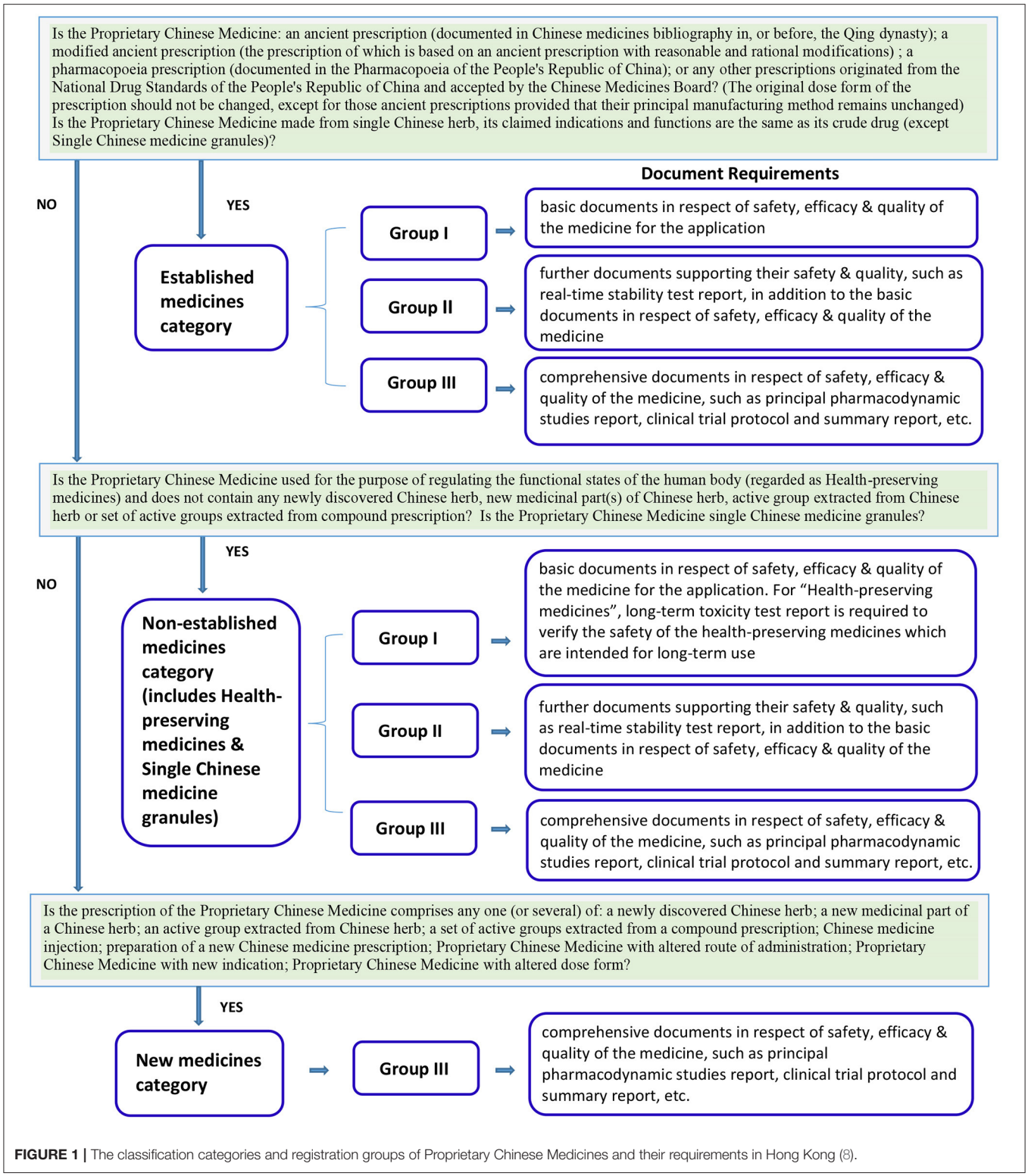


FIGURE 1 | The classification categories and registration groups of Proprietary Chinese Medicines and their requirements in Hong Kong (8).

acids and many different traditional medicines including most Proprietary Chinese Medicine. Proprietary Chinese Medicine can be registered under a Class I or Class II or Class III product license (9) (see **Figure 2**). For example, Proprietary Chinese Medicines which meet the Compendial requirements may submit an application under Class I. The well-defined application guidelines help applicants to determine the right type and class of the product license for which they should apply. If in doubt,

TABLE 1 | Product license application requirements summary for Hong Kong and Canada (5, 9).

		Group I/Class I	Group II/Class II	Group III/Class III
Hong Kong	Established medicines category	Basic documents **Product safety documents** 1. Heavy metals and toxic elements test report 2. Pesticide residues test report 3. Microbial limit test report 4. Acute toxicity test report 5. Long-term toxicity test report 6. Local toxicity test report 7. Summary report on product safety documents **Product efficacy documents** 1. Interpretation and principle of formulating a prescription 2. Reference materials on product efficacy 3. Summary report on product efficacy documents **Product quality documents** 1. Manufacturing method 2. Physicochemical properties of crude drugs 3. Product specification, method and certificate of analysis 4. Accelerated stability test report or general stability test report	Further documents **Product safety documents** 1. Heavy metals and toxic elements test report 2. Pesticide residues test report 3. Microbial limit test report 4. Acute toxicity test report 5. Long-term toxicity test report 6. Local toxicity test report 7. Mutagenicity test report 8. Carcinogenicity test report 9. Reproductive and development toxicity test report 10. Summary report on product safety documents **Product efficacy documents** 1. Interpretation and principle of formulating a prescription 2. Reference materials on product efficacy 3. Summary report on product efficacy documents **Product quality documents** 1. Manufacturing method 2. Physicochemical properties of crude drugs 3. Product specification, method and certificate of analysis 4. Real-time stability test report	Comprehensive documents **Product safety documents** 1. Heavy metals and toxic elements test report 2. Pesticide residues test report 3. Microbial limit test report 4. Acute toxicity test report 5. Long-term toxicity test report 6. Local toxicity test report 7. Mutagenicity test report 8. Carcinogenicity test report 9. Reproductive and development toxicity test report 10. Summary report on product safety documents **Product efficacy documents** 1. Interpretation and principle of formulating a prescription 2. Reference materials on product efficacy 3. Principal pharmacodynamic studies report 4. General pharmacological studies report 5. Clinical trial protocol and summary report 6. Summary report on product efficacy documents **Product quality documents** 1. Manufacturing method 2. Physicochemical properties of crude drugs 3. Product specification, method and certificate of analysis 4. Real-time stability test report
	Non-established medicines category New medicines category			
Canada	Compendial (NHPD) Monograph)	- NNHPD Label text - Evidence (Attestation to a NNHPD monograph) - Animal Tissue form - Finished Product Specifications (Upon request only)		
	Traditional		- NNHPD Label text - Quality Summary Report: Characterization, identification and quantification standards; Purity standards General indicators for quality and Performance Tests - Safety Evidence: extensive history of use; Cautions, warnings and contra-indications; no new, unknown safety concerns have been identified. Efficacy Evidence: Pharmacopoeial Evidence- a NNHPD monograph or from a recognized pharmacopeia; Minimum of two other traditional references - Independent references; authoritative references and from a reputable source; an expert opinion as second reference. - Animal Tissue form - Finished Product Specifications	Full assessment required: - NNHPD Label text - Quality Summary Report: Characterization, identification and quantification standards; Purity standards General indicators for quality and Performance Tests - Safety Evidence: extensive history of use; Cautions, warnings and contra-indications; no new, unknown safety concerns have been identified. Efficacy Evidence: Pharmacopoeial Evidence - a NNHPD monograph or from a recognized pharmacopeia; Minimum of two other traditional references - Independent references; authoritative references and from a reputable source; an expert opinion as second reference. - Animal Tissue form - Finished Product Specifications
	General (Non-traditional)		Low or Medium risk Proprietary Chinese Medicine - NNHPD Label text - Quality Summary Report: Characterization, identification and quantification standards; Purity standards General indicators for quality and Performance Tests - Evidence/Safety Summary Report: Phase II clinical trials; Epidemiological studies; Pilot and open label studies; Reputable textbooks; Systematic review other than meta-analysis; Published, peer-reviewed, detailed narrative reviews which cite detailed primary evidence; Published compilations referring to traditional use etc., - Evidence (Minimum two pieces) - Animal Tissue form - Finished Product Specifications	High risk Proprietary Chinese Medicine, full assessment required: - NNHPD Label text - Quality Summary Report: Characterization, identification and quantification standards; Purity standards General indicators for quality and Performance Tests - Evidence/Safety Summary Report: NNHPD published monographs; Phase III or phase IV clinical trials (randomized, controlled, well-designed); Meta-analysis (controlled and well-designed); Prospective observational studies or combinations of one prospective study and one retrospective study; Evidence of a positive decision from another regulatory agency - Evidence (Minimum two pieces) - Animal Tissue form - Finished Product Specifications

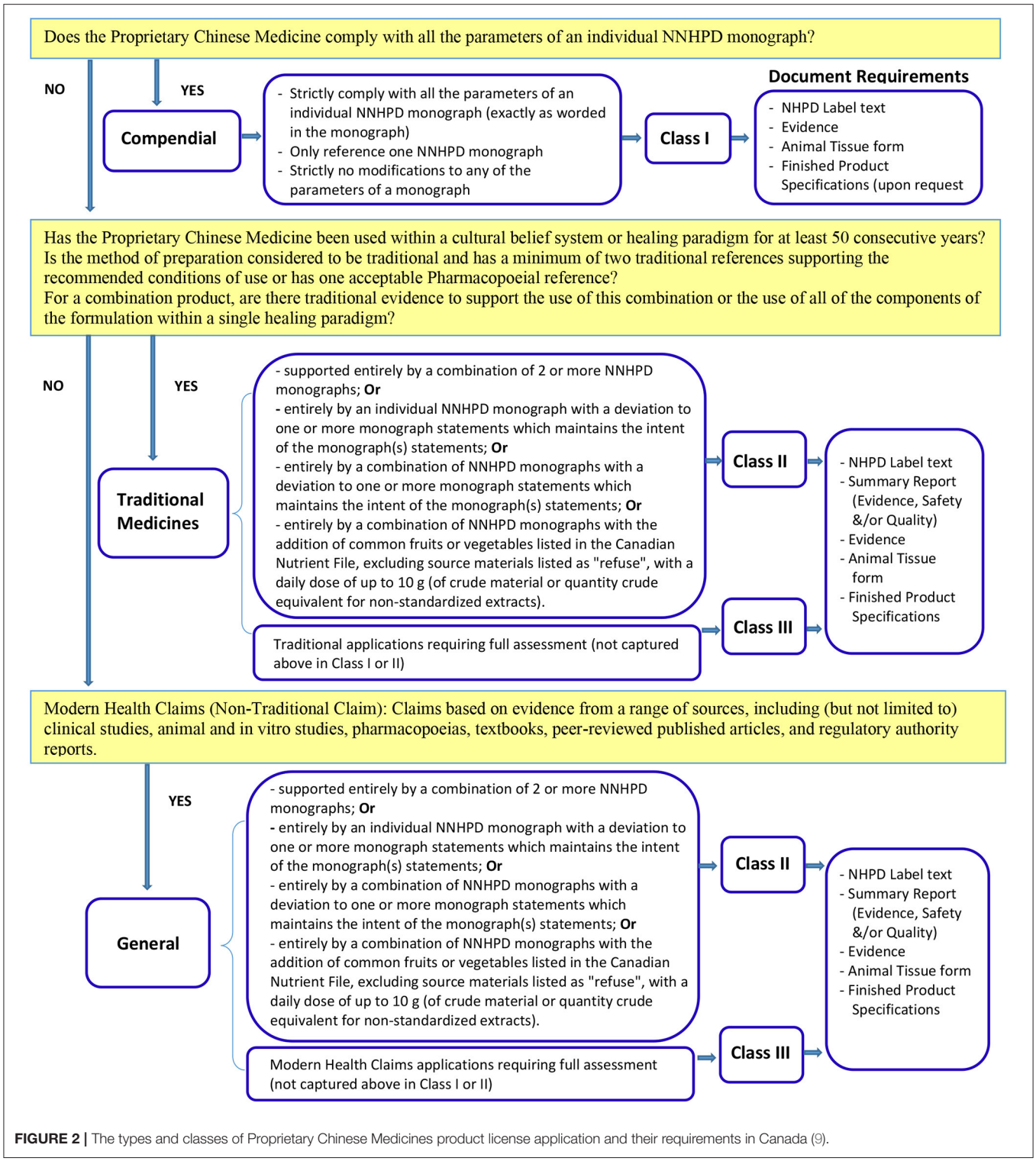


FIGURE 2 | The types and classes of Proprietary Chinese Medicines product license application and their requirements in Canada (9).

applicants can request a Pre-submission Meeting to clarify the type of application required (9). In addition, if after reviewing all relevant regulations, guidance and tools, an applicant is unsure if a product is suitable for licensing as a natural health product, the applicant is encouraged to submit a product classification request prior to submitting a product licensing application. It should be noted that in the Canadian system, at least one "claim" must be approved as part of the licensing application. Recognizing that many Proprietary Chinese Medicines may be used for a wide variety of conditions (representing different claims), the regulatory system, which requires additional documentation for applications in Classes 2 and 3, creates an incentive for applicants

to seek approval for a single claim in the lowest Class possible with the least regulatory burden.

STRUCTURED (QUALITY, SAFETY, AND EFFICACY) REQUIREMENTS OF PROPRIETARY CHINESE MEDICINES IN HONG KONG AND CANADA

Hong Kong

For Proprietary Chinese Medicines in the "Established medicines category" and "Non-established medicines category" to be registered under Group I, basic documents related to safety, efficacy & quality of the medicine are required for the application. For "Health-preserving medicines" in the "Non-established medicines category," a long-term toxicity test is required to verify safety because these products are intended for long-term use.

For Proprietary Chinese Medicines in the "Established medicines category" and "Non-established medicines category" to be registered in Group II, further documents supporting their safety and quality are required, such as real-time stability testing, in addition to the basic documents related to the safety, efficacy, and quality of the medicine.

For Proprietary Chinese Medicines under the "Established medicines category," "Non-established medicines category," and "New medicines category" to be registered in Group III, comprehensive documents documenting the safety, efficacy, and quality of the medicine are required, such as principal pharmacodynamic studies, clinical trial protocol, and summary report, etc. (8).

Canada

The Natural and Non-prescription Health Products Directorate (NNHPD) requests that applicants identify the class under which they are applying in the cover letter of their application according to the definitions. If a Class is not identified correctly in the cover letter, the application will be refused.

By attesting to a monograph, the applicant is confirming that the application meets all of the monograph parameters (Class I) to which the applicant has attested. If applicants are not attesting to full monograph parameters in Class II or III applications, they must ensure that evidence or a rationale for not attesting to the monograph has been provided.

The details of the quality, safety and efficacy requirements for Hong Kong and Canada are listed in **Tables 2–4**, respectively (10–16).

IMPACT OF REGULATIONS IN HONG KONG AND CANADA

Product regulations are the gates defending public health against health products without proven quality, safety, and effectiveness. They should ensure minimum quality of products provide the basis for quick action if post marketing reports identify issues with specific products. Although there is no international

TABLE 2 | The quality requirements of proprietary Chinese medicines in Hong Kong and Canada (10, 11).

Requirements	
Hong Kong	**Canada**
INDIVIDUAL PRODUCT QUALITY DOCUMENT	
1. Manufacturing Method (1) Processing procedure for each raw herb (2) Names and quantities of all excipients used in the processes (3) Specified technical controls for procedures that may affect the quality of the Proprietary Chinese Medicine	**1. Characterization** **A. Chemicals** **B. Processed ingredients** (1) Process characterization of crude materials (2) Process characterization for highly processed ingredients **C. Extracts** (1) Standardized extracts (2) Fortified extracts
2. Physicochemical Properties of Crude Drugs **A. The crude drug(s) of a Proprietary Chinese Medicine** (1) A newly-discovered Chinese herb (2) A new medicinal part of a Chinese herb (3) An active group extracted from Chinese herb (4) A set of active groups extracted from a compound prescription (i) Description (ii) Identification Method (iii) Inspection (iv) Assay **B. Crude herbs of the Proprietary Chinese Medicine that do not fall into any of the four groups as mentioned above in (A)**	**2. Physicochemical Properties of Raw Material** **A. Identification Tests of the ingredients** (1) Appropriate Identification of botanical products (2) Appropriate identification of specific medicinal ingredients (3) Identity testing on the finished product **B. Quantity** (1) Quantification by assay (2) Quantification by input **C. Purity Standards** **D. Additional Tests & Criteria** (1) General Indicators for Quality (2) Performance Tests (3) Analytical testing and requirements to support label claims (4) Reduced testing schedules that are captured on specifications (5) Antimicrobial effectiveness testing Where an NNHPD monograph exists for an ingredient, the specification section of the monograph should be consulted
3. Finished Product Specification, Methods & Certificate of Analysis **A. Product specification** (1) Description (2) Identification (3) Assay (4) Inspection **B. Test Methods** **C. Test Report**	**3. Finished Product Specification and Test Methods** **A. Product specification** (1) Physical description (2) Identity testing on the finished product (3) The finished product specifications **B. Test Methods**
4. Stability Test Report	**4. Stability Test Report**
REQUIREMENTS FOR TEST LABORATORIES	
(1) Met the requirements set by the International Standardization Organization (i.e. ISO/IEC 17025) (2) Good Laboratory Practice (GLP) (3) Other laboratories accepted by the Board	Good Laboratory Practice (GLP)

Detailed requirements are listed in ***Supplementary Material 1****.*

TABLE 3 | The safety requirements and purity standards (under Quality Requirements' guidelines) of proprietary Chinese medicines in Hong Kong and Canada respectively (11, 12).

Hong Kong (Safety requirements)	Canada (Purity standards)
Documents supporting the safety claims of the product are required to be submitted to the Chinese Medicines Board for assessments. The documents shall include the basic and toxicological tests. Other reference material may be provided to support the safety claims of the products, e.g., the published bibliography or monographs, etc.	Safety Requirements: - supported by its history of use (at least 50 consecutive years of traditional use within a cultural health system or paradigm) and no new, unknown safety concerns outside of evidence for traditional use. Two independent references - Modern Health Claims are based on the identified risks to health. Evidence recommendations are categorized into low, medium, and high risk. Within any risk category, the evidence may be sufficient to support both safety and efficacy when it is appropriate for the claim and when it fully reflects the product's recommended conditions of use. For the low and medium categories, methodologically weak safety evidence should be supplemented to demonstrate consistency in results and plausibility. For high risk category, product specific evidence is recommended with a complete critical summary reflecting the totality of evidence that usually reflect more than one type of evidence. Due to the test requirements' similarity, in this comparative study we compare the safety requirements of Proprietary Chinese Medicine product in Hong Kong to the product's purity standard in Canada.
A. Heavy metals and toxic element test Heavy metals (mercury, lead & cadmium) or toxic elements (arsenic)	**A. Chemical Contaminants** Elemental impurities (Catalysts and environmental contaminants); Topical products
B. Pesticide residues test	**B. Pesticide residues**
C. Microbial limit test Total aerobic count, molds & yeast count & the presence of specified bacteria	**C. Microbial Contaminants** Multi-Component products, products in liquid dosage form.
D. Acute toxicity test Median lethal/Maximum tolerable dose	**D. Other Impurities** (1) Mycotoxins (e.g., aflatoxins) Testing (2) Cyanobacterial toxins (e.g., microcystins) (3) Solvent residues (4) Hormone testing of animal materials (5) Incidental impurities, related substances and process impurities (6) Potential adulterants in natural health products
E. Long-term toxicity test	
F. Local toxicity test Local dermal toxicity/Mucous membrane irritation test	
G. Mutagenicity test For Group II & Group III application to examine the carcinogenicity or reproductive toxicity: Bacterial reverse mutation test, chromosomal aberration test with mammalian cells in culture & micronucleus test with rodents	
H. Carcinogenicity test For Group II & Group III application to examine the carcinogenicity or tumorigenicity: Preliminary carcinogenicity study & full-scale carcinogenicity study	
I. Reproductive and development toxicity test For Group II & Group III application only, to examine any toxic effects on animal's reproductivity and teratogenic effect on their offspring: General reproductive toxicity, teratogenicity & perinatal toxicity test	
J. Requirements for test laboratories International Standardization Organizations, Chinese Medicines Board, State Food & Drug, or Chinese Medicines Board	**E. Requirements for test laboratories** - Good Laboratory Practice (GLP)
K. Summary report of product safety documents Overall conclusion; a reasonable assessment	**F. Summary report of product safety documents** Safety Overview; risk Information and Risk Mitigation

Detailed requirements are listed in ***Supplementary Material 2****.*

standard for regulation for Proprietary Chinese Medicines, the regulatory authorities of Hong Kong and Canada have both adopted a multi-pronged regulatory strategy by dividing applications into groups and classes.

In Hong Kong since registration of Proprietary Chinese Medicines took effect in 2003, more than 2,400 Proprietary Chinese Medicines products have been issued a certificate of registration (17). The registered products not only provide safe Chinese Medicine products to the public, but also have driven ancillary economic activities and created employment opportunities. In 2019, the Hong Kong government established the Hong Kong Chinese Medicine Development Fund with HKD 500 million to promote the development of the Chinese Medicine including support to enhance the overall standard of the industry (18). Manufacturers of Proprietary Chinese Medicines can apply the fund to design or purchase equipment that meets the requirements of Chinese Medicine Manufacturing Quality Management (GMP) (19). Moreover, the government will provide a list of accredited testing institutes to assist manufacturers to meet technical requirements and

TABLE 4 | The efficacy requirements of proprietary Chinese medicines in Hong Kong and Canada (11, 13).

Requirements	
Hong Kong	**Canada**
1. Reference materials on product efficacy Including reference literature or documentary proofs on long history of use (i) Established medicines category (ii) Non-established medicines category - Health-preserving medicines - Single Chinese medicine granules (iii) New medicines category	**1. Evidence requirements for safety and efficacy** The safety and efficacy of health claims associated with NHPs must be supported by appropriate evidence such as clinical trial data to references to published studies, journals, pharmacopeias and traditional resources. The type and amount of supporting evidence required is dependent on the proposed health claim of the product and its overall risks. The evidence requirements for efficacy are listed depending on whether the product is a: - Traditional Medicine; - NHP with Traditional use claims or with Modern Health Claims
2. Interpretation and principle of formulating a prescription - written by professionals - efficacy and safety - General requirements: Source, ingredients, specified usage and dosage of the preparation, functions & indications, interpretation, precautions (if any)	**2. Efficacy Evidence for Traditional Medicines** **A. Pharmacopoeial Evidence for Traditional Medicines** - relevant pages of a monograph from a recognized pharmacopeia; - a monograph published by a reputable agency with a definition of traditional medicines comparable to that of the NNHPD **B. Other Types of Efficacy Evidence for Traditional Medicines** at least 2 independent references that support the recommended conditions of use; an expert opinion if only 1 reference
3. Principal pharmacodynamic studies For Group III application only: Brief requirements, requirements for test laboratories **4. General pharmacological studies** For Group III application only: Brief requirements, requirements for test laboratories **5. Clinical trial protocol and summary report** For Group III application only. (i) Brief requirements (a) Phases of clinical trials (b) Contents of clinical trial protocol (c) Contents of the summary report of clinical trials (d) Documents to be submitted upon application (ii) Requirements for Clinical Trial centers	**3. Efficacy Evidence Recommendations for NHPs with Modern Health Claims** **A. Efficacy Evidence for the High-Risk Category** complete critical summary; systematic review; demonstrate statistically significant outcomes; additional evidence **B. Efficacy Evidence for the Medium Risk Category** Evidence as individual references: **C. Efficacy Evidence Requirements for the Low Risk Category** For minor health conditions & diseases; treatment of symptoms or risk factors of serious or major conditions or the risk reduction of these conditions; general health maintenance, support, or promotion that refers to modification of a biochemical or physiological function of a nutritional nature or implies benefit to a minor disease or health condition. Evidence to reflect the low-risk nature This category includes most vitamins, minerals, essential nutrients, and other nutrients recommended for use by healthy adults.
6. Summary report on product efficacy documents An overall conclusion and a reasonable assessment of product efficacy.	**4. Summary report on product efficacy documents** Consists of: recommended use or purpose (health claim); critical overview organized based on the claims of the product; dosage and Other Conditions of Use

Detailed requirements are listed in ***Supplementary Material 3****.*

provide required documentation throughout the registration process (20).

In 2012, Canada established guidelines regarding product license application for traditional medicines including Chinese Medicine. Noteworthily, instead of evidence for ingredients that are already known to be safe and efficacious, Canada's regulatory approach allows assessment of traditional medicines based on efficacy and safety data from relevant traditional healing paradigms (21). However, Proprietary Chinese Medicines that consist of modified or inconsistent Chinese Medicine classical formulae are not eligible for this regulatory pathway and require detailed safety or efficacy documentation. For products that are eligible for Class I, manufacturers must attest that they are manufacturing the product according to the requirements outlined in the Canadian monograph which is based on the Canadian regulatory authority's review of the evidence and determination of what is required to ensure a product is safe and of sufficient quality (22).

TAKING ONE PROPRIETARY CHINESE MEDICINE AS AN EXAMPLE: ZHIZHU KUANZHONG (ZZKZ) CAPSULE

ZZKZ Capsule (SFDA approval number Z20020003; NPN approval number 80104354), manufactured by Shuangren Pharmaceutical Co., Ltd. of Lonch Group, has been marketed for more than 10 years in China. This Proprietary Chinese Medicine originates from the traditional prescription "Zhizhu Decoction." ZZKZ Capsule is mainly composed of the following four commonly used Chinese herbs: Rhizoma Atractylodis Macrocephalae (plant *Atractylodes macrocephala* Koidz.),

TABLE 5 | Zhizhu Kuanzhong Capsule - product license application in Hong Kong and Canada (8, 9).

No.	Requirements	Hong Kong (Application no.: Z20020003)	Canada (Application no.: 80104354)
1	Product License Application Category	Established medicines category	Compendial - Traditional
2	Product License Application Group	Group I	Class I
3	Product License Application Form	✓	✓
4	Evidence	**Product safety documents** 1. Heavy metals and toxic elements test report 2. Pesticide residues test report 3. Microbial limit test report 4. Acute toxicity test report 5. Long-term toxicity test report 6. Local toxicity test report 7. Summary report on product safety documents **Product efficacy documents** 1. Interpretation and principle of formulating a prescription 2. Reference materials on product efficacy 3. Summary report on product efficacy documents **Product quality documents** 1. Manufacturing method 2. Physicochemical properties of crude drugs 3. Product specification, method and certificate of analysis 4. Accelerated stability test report or general stability test report	Attest to a NNHPD Product Monograph from the Compendium of Monographs: Traditional Chinese Medicine Ingredients
5	Label text	✓	✓
6	Animal Tissue form	X	X

Fructus Aurantii Immaturus (plant *Citrus* × *aurantium* L.), Radix Bupleuri (plant *Bupleurum chinense* DC.), and Fructus Crataegi (plant *Crataegus pinnatifida* Bunge). The combination of these four herbs is commonly used to treat spleen deficiency, qi stagnation, liver-stomach disharmony as well as stomach duct and abdomen fullness within the traditional Chinese medicine paradigm (23). To illustrate the similarities and differences between the two regulatory processes, we summarized the requirement of documents for ZZKZ Capsule to register in both Hong Kong (Group I) and Canada (Class I) in **Table 5**.

Regulation in Hong Kong requires six different safety test reports including heavy metals and toxic elements report, pesticide residues report, microbial limit test report, etc. A summary of evidence including reference materials is required to support product efficacy. In addition, details of the manufacturing method, product specifications and stability testing are required.

In contrast, regulation in Canada requires confirmation that all ingredients are listed in the relevant tables of acceptable Traditional Chinese Medicine Ingredients in the Compendium of Monographs and attestation from the manufacturer that the product is manufactured according to the preparations and methods of processing outlined in one of five specific approved reference pharmacopeias/texts. Similarly, conditions of use and adverse effects identified on the label must be consistent with those outlined in one of the five acceptable reference pharmacopeias (24).

Thus, Hong Kong and Canada take very different approaches to the regulation of the same product which appear to entail very different amounts of effort, time and money on the part of manufacturers who wish to obtain a license to market the same product. This creates a "natural experiment" that would be worth investigating to explore which regulatory approach is the most efficient at supporting the licensing of safe, effective and high quality products available for consumers.

DISCUSSION

One of the biggest challenges facing manufacturers is the lack of consistency of regulatory requirements globally. In some cases, the documentation required is very similar; in other cases, it varies dramatically. The classification criteria for Proprietary Chinese Medicines registration are different in Hong Kong and Canada but both involve judgements based on historic records of Proprietary Chinese Medicines and include evidence of safety, efficacy and quality. What differs is the type of evidence that must be submitted.

For example, for Proprietary Chinese Medicines that qualify for registration in Group I (Hong Kong), manufacturers are asked to provide safety and efficacy data including product specification, toxicity test report and stability test report. In contrast, for a similar category of products (Class I) in Canada, manufacturers are only required to submit documentation that the Proprietary Chinese Medicines will be manufactured and used in line with traditional data and in strict compliance with all the parameters of a specific NNHPD

monograph recognized by the Health Canada. It includes the information from Pharmacopeia published by a reputable agency (e.g., the Pharmacopeia of the People's Republic of China or translated version of the Drug Standard of People' Republic of China), ensures that there are sufficient data to demonstrate the quality, safety and efficacy of the Proprietary Chinese Medicines.

Applications for Proprietary Chinese Medicines that fall into the "non-established" or "new medicines" category in Hong Kong, and under the "modern health claims" category in Canada, will be assessed under the requirements outlined for Group III in Hong Kong and under requirements of Class II or Class III in Canada. The requirements in the two countries for these kinds of products also differ. For example, in Hong Kong, clinical trials with the new indications will required to be conducted in the Hong Kong population before registration. In Canada, depending on the health risk of the Proprietary Chinese Medicine, the claimed therapeutic functions or efficacy must be supported by evidence from the health care literature (including traditional Chinese medicine literature), by research studies assessing product efficacy including clinical trials, and/or a complete critical summary of a systemic review reflecting the totality of evidence.

The safety requirements for chemical contaminants such as heavy metals and toxic elements, pesticide residues and microbial contaminants are similar in Hong Kong and Canada, but there are important differences (**Supplementary Material 2**). For example, Hong Kong has put emphasis on the some toxicity tests including the mutagenicity test and the reproductive and development toxicity test, as well as dose related toxicity tests; whereas Canada has more emphasis on testing for impurities that may cause toxicity, such as mycotoxins, solvent residues and incidental impurities, related substances and process impurities. Canada also has listed clear guidelines on the performance tests of the finished products (11, 12). These differences significantly increase the time and cost burden to manufactures hoping to license/register products in multiple jurisdictions.

Finally, Proprietary Chinese Medicines manufacturers raise concerns about inconsistent requirements from regulatory authorities with respect to packaging and labeling (25). In 2020, the regulatory body in Hong Kong updated guidelines regarding labels and package inserts of Proprietary Chinese Medicines (26, 27) while requirements on labeling and packaging for Proprietary Chinese Medicines are comparatively less specified in Canada (28).

As a component of traditional medicine, Proprietary Chinese Medicines create unique challenges for regulators in countries outside those where the products are traditionally used due to their complex nature and use within health paradigms that differ from Western biomedicine. It appears that safety and quality parameters may be the easiest to think about harmonizing as these parameters may be the least impacted by health paradigm differences. Agreement across regulators regarding which tests are required/acceptable to prove safety and quality would significantly increase the efficiency of the regulatory process for both manufacturers and regulators (**Supplementary Material 3**). With the development of global standards on submission, review and authorization of these products, manufacturers could submit the same testing data to multiple regulatory agencies. And regulatory agencies could consider fast tracking the review of products that were already approved in other countries that share similar standards.

CONCLUSION

Knowledge of the Proprietary Chinese Medicines product license application procedure and requirements in Hong Kong and Canada, and understanding their similarity and differences will enable the applicants to develop an appropriate strategy for gaining product approval. Exploring ways to harmonize the regulatory process has potential to benefit manufacturers, regulators, and patients by increasing efficiency and decreasing costs.

AUTHOR CONTRIBUTIONS

LZ and HB shared the idea and supervised the study. WL collected policy documents from regulatory bodies and added the figures and tables. All authors were involved in drafting and revising the manuscript, reviewed, and approved the final manuscript.

FUNDING

This work was supported by a Visiting Professorship fund from the Leslie Dan Faculty of Pharmacy, University of Toronto, Faculty Research Fund (FRG2/16-17/094) from Hong Kong Baptist University and Special Research on Modernization of Traditional Chinese Medicine in the National Key Research and Development Program in China's 13th Five-Year Plan Demonstrative Research International Clinical Study of Zhizhu Kuanzhong Capsule (2017YFC1703703).

ACKNOWLEDGMENTS

We thank Ms. Sonia Low for translation and collection all the government's documents.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.617625/full#supplementary-material

REFERENCES

1. Franklin JM, Glynn RJ, Martin D, Schneeweiss S. Evaluating the use of nonrandomized real-world data analyses for regulatory decision making. *Clin Pharmacol Ther*. (2019) 105:867–77. doi: 10.1002/cpt.1351
2. Eichler HG, Baird LG, Barker R, Bloechl-Daum B, Børlum-Kristensen F, Brown J, et al. From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients. *Clin Pharmacol Ther*. (2015) 97:234–46. doi: 10.1002/cpt.59
3. World Health Organization. *Traditional, Complementary and Integrative Medicine*. (2020). Available online at: https://www.who.int/health-topics/traditional-complementary-and-integrative-medicine#tab=tab_1 (accessed 6 October, 2020).
4. Chinese Medicine Council of Hong Kong. *Guidance Notes on "How to Classify Products as Proprietary Chinese Medicines"*. (2011). Available online at: https://www.cmchk.org.hk/pcm/pdf/class_guide_trade_ref_e.pdf (accessed 6 October, 2020).
5. Chinese Medicine Council of Hong Kong. *Registration of Proprietary Chinese Medicines*. (2020). Available online at: https://www.cmchk.org.hk/pcm/eng/#main_down02.htm (accessed 6 October, 2020).
6. Health Canada. *Natural Health Products*. (2020). Available online at: https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription.html (accessed 6 October, 2020).
7. Government of Canada. *Natural Health Products Regulations*. (2020). Available online at: https://laws-lois.justice.gc.ca/eng/regulations/sor-2003-196/page-1.html (accessed 6 October, 2020).
8. Chinese Medicine Council of Hong Kong. *Registration of Proprietary Chinese medicines: Application Handbook*. (2020). Available online at: https://www.cmchk.org.hk/pcm/pdf/reg_handbook_bfver_e.pdf (accessed 6 October, 2020).
9. Health Canada. *Natural Health Products Management of Applications Policy*. (2019). Available online at: https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/natural-health-products/legislation-guidelines/guidance-documents/management-product-licence-applications-attestations/nhp-map-2019-guidance-document-eng.pdf (accessed 6 October, 2020).
10. Chinese Medicine Council of Hong Kong. *Registration of Proprietary Chinese Medicine: Product Quality Documents Technical Guidelines*. (2004). Available online at: https://www.cmchk.org.hk/pcm/pdf/guide_quality_e.pdf (accessed 6 October, 2020).
11. Health Canada. *Quality of Natural Health Products Guide*. (2015). Available online at: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodnatur/legislation/docs/eq-paq-eng.pdf (accessed 6 October, 2020).
12. Chinese Medicine Council of Hong Kong. *Registration of Proprietary Chinese Medicine: Product Safety Documents Technical Guidelines*. (2004). Available online at: https://www.cmchk.org.hk/pcm/pdf/guide_save_e.pdf (accessed 6 October, 2020).
13. Chinese Medicine Council of Hong Kong. *Registration of Proprietary Chinese Medicine: Product Efficacy Documents Technical Guidelines*. (2004). Available online at: https://www.cmchk.org.hk/pcm/pdf/guide_work_e.pdf (accessed 6 October, 2020).
14. Chinese Medicine Council of Hong Kong. *Appendices: Product Quality Documents Technical Guidelines*. (2004). Available online at: https://www.cmchk.org.hk/pcm/pdf/guide_quality_n_e.pdf (accessed 6 October, 2020).
15. Chinese Medicine Council of Hong Kong. *Appendices: Product Safety Documents Technical Guidelines*. (2004). Available online at: https://www.cmchk.org.hk/pcm/pdf/guide_save_n_e.pdf (accessed 6 October, 2020).
16. Chinese Medicine Council of Hong Kong. *Appendices: Product Efficacy Documents Technical Guidelines*. (2004). Available online at: https://www.cmchk.org.hk/pcm/pdf/guide_work_n_e.pdf (accessed 6 October, 2020).
17. Chinese Medicine Council of Hong Kong. *Lists of Applications for Proprietary Chinese Medicine Registration*. (2020). Available online at: https://www.cmchk.org.hk/pcm/eng/#main_listpcm_2018.htm (accessed 6 October, 2020).
18. The Government of the Hong Kong Special Administrative Region. *Press Releases: Chinese Medicine Development Fund launched today*. (2019). Available online at: https://www.info.gov.hk/gia/general/201906/25/P2019062500526.htm?fontSize=1 (accessed 6 October, 2020).
19. Chinese Medicine Development Fund. *Proprietary Chinese Medicine Quality and Manufacturing System Enhancement Funding Scheme (A2)*. (2020). Available online at: https://www.cmdevfund.hk/content-en.php?mid=3&id=17 (accessed 6 October, 2020).
20. Chinese Medicine Regulatory Office of the Department of Health. *Government Chinese Medicines Testing Institute (GCMTI)*. (2020). Available online at: https://www.cmro.gov.hk/html/eng/GCMTI/org_chart.html (accessed 6 October, 2020).
21. Health Canada. *Pathway for Licensing Natural Health Products used as Traditional Medicines, Version 1.0*. (2012). Available online at: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodnatur/legislation/docs/tradit-eng.pdf (accessed 6 October, 2020).
22. Health Canada. *Compendium of Monographs*. (2009). Available online at: https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/applications-submissions/product-licensing/compendium-monographs.html (accessed 6 October, 2020).
23. Wen MY, Zhang FC, Wang YJ. Effect of Zhizhu Kuanzhong Capsules on treatment of functional dyspepsia: a meta-analysis of randomized controlled trials. *Chin J Integr Med*. (2019) 25:625–30. doi: 10.1007/s11655-018-2846-0
24. Health Canada. *Traditional Chinese Medicine Ingredients (TCMI)*. (2015). Available online at: http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=tcm&lang=eng (accessed 6 October, 2020).
25. Office of The Ombudsman HK. *Direct Investigation Report: Government's Regulation of Proprietary Chinese Medicine*. (2018). Available online at: https://ofomb.ombudsman.hk/abc/files/2018_12_FR___3.pdf (accessed 6 October, 2020).
26. Chinese Medicine Council of Hong Kong. *Guidelines on Labels of Proprietary Chinese Medicines*. (2020). Available online at: https://www.cmchk.org.hk/pcm/pdf/gl_pcm_e.pdf (accessed 6 October, 2020).
27. Chinese Medicine Council of Hong Kong. *Guidelines on Package Inserts of Proprietary Chinese Medicines*. (2020). Available online at: https://www.cmchk.org.hk/pcm/pdf/gp_pcm_e.pdf (accessed 6 October, 2020).
28. Health Canada. *Forward Regulatory Plan 2019-2021: Self-Care Framework*. (2020). Available online at: https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/self-care-framework.html (accessed 6 October, 2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 01 July 2021
doi: 10.3389/fmed.2021.619513

The Use of Remote Monitoring Technologies: A Review of Recent Regulatory Scientific Advices, Qualification Opinions, and Qualification Advices Issued by the European Medicines Agency

Marieke J. H. J. Dekker[1], Pieter Stolk[2] and Anna M. G. Pasmooij[1] on behalf of the RADAR-AD[†]*

[1] *Medicines Evaluation Board, Utrecht, Netherlands,* [2] *Lygature, Utrecht, Netherlands*

OPEN ACCESS

Edited by:
Bruno Sepodes, University of Lisbon, Portugal

Reviewed by:
Spiros Vamvakas, European Union, Belgium
Rolf Bass, Retired, Berlin, Germany

****Correspondence:***
Anna M. G. Pasmooij
am.pasmooij@cbg-meb.nl

[†]*www.radar-ad.org*

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *20 October 2020*
Accepted: *21 May 2021*
Published: *01 July 2021*

Citation:
Dekker MJHJ, Stolk P and Pasmooij AMG (2021) The Use of Remote Monitoring Technologies: A Review of Recent Regulatory Scientific Advices, Qualification Opinions, and Qualification Advices Issued by the European Medicines Agency. Front. Med. 8:619513. doi: 10.3389/fmed.2021.619513

Aims: Recently, the use of novel remote monitoring technologies (RMTs) in trials has gained much interest. To facilitate regulatory learning, we evaluated qualification opinions (QOs) and advices (QAs) and scientific advices (SAs) of the Committee for Medicinal Products for Human Use (CHMP) to gain insight in the types of devices that are intended to be used in clinical trials for supporting/submitting application for obtaining marketing authorization (registration trials) and the main recommendations of the CHMP.

Methods: QOs, QAs, and SAs of the CHMP that assessed RMTs between 2013 and 2019 were eligible for our study. The following information was extracted from the documents: year of advice/opinion, device and endpoints used, type of endpoint (primary, secondary, exploratory, or safety), and main recommendations of the CHMP.

Results: In total two QOs, four QAs, and 59 SAs were included in our study (total of SAs between 2013 and 2019 = 4,054). In the SAs, accelerometers to measure activity and/or sleep parameters ($n = 31$) were the most frequently used devices, followed by mobile applications ($n = 6$) and glucose monitoring devices ($n = 6$). Usually, these measures were proposed as secondary or exploratory endpoints ($n = 32$). The main recommendations of the CHMP were related to relevance of the (novel) outcome measure; validation; precision, accuracy, sensitivity, and specificity; compliance; sampling interval; and data handling and privacy.

Conclusions: Although there was a trend toward an increased use over time, the use of RMTs in registration trials is still relatively rare. In the absence of formal European regulatory guidance on mHealth technologies, insight in the main recommendations of the CHMP may stimulate the use of novel RMTs in a regulatory context.

Keywords: remote monitoring devices, European Medicine Agency, scientific advices, qualification advices, qualification opinions

INTRODUCTION

In recent years, remote monitoring technologies (RMTs) have rapidly evolved and gained increasing interest of health technology industry, clinicians, medicine developers, and regulators (1). Several public–private initiatives have emerged that provide platforms for collaborations between patient, clinical, and research communities as well as mHealth companies to promote new developments, provide guidance, and take patient and consumers views into account. The Duke Margolis Center, for example, convened a working group of experts, including the Food and Drug Administration (FDA) and released a set of recommendations on how to promote efficient and ethical research-capable technologies such as mHealth apps and wearables for real-world evidence generation (2).

RMTs offer new opportunities to assess novel endpoints or possibly better ways to measure existing endpoints. With these technologies, endpoints can be assessed in the home environment, which has several advantages. For example, measurements are less time point dependent and are able to capture fluctuations in disease activity and activity patterns, such as differences between weekdays and weekends. Next to this, less visits to clinics are necessary, which may decrease participation burden and promote participation. Furthermore, endpoints can be assessed with high frequency, which improves data completeness and sensitivity. Lastly, RMTs offer objective ways for real-time outcome measurement and may reduce white coat effects.

From a regulatory perspective, it is important that novel endpoints are reliable, accurate, sensitive to change, and validated for purpose of use. The Clinical Trials Transformation Initiative (CTTI), a collaboration between pharma companies, academics, and the FDA, issued recommendations on the development of novel endpoints generated by mobile technology for use in clinical trials (3). These recommendations focus on optimizing novel endpoint selection as well as practical approaches to the novel endpoint development process. In Europe, the Heads of Medicines Agency (HMA)/European Medicines Agency (EMA) Task Force on Big Data has released a subgroup report on "Social Media and M-Health Data" that explored social media sites and mHealth technologies that could be valuable to support medicine regulation decision-making and its main challenges in using these data for regulatory purposes (1). Furthermore, as of June 2020, the EMA published *Questions and Answers (Q&A): Qualification of digital technology-based methodologies to support approval of medicinal products* (4). This Q&A document does not contain comprehensive guidance but reflects the EMA's current experience, and further considerations may be added as the EMA's experience increases. However, it does provide some important recommendations to consider for successful qualification of digital technology-based methodologies.

In the European regulatory context, the EMA provides three different procedures for device manufacturers and pharma companies to obtain feedback from the Committee for Medicinal Products for Human Use (CHMP). First, a qualification opinion (QO) issues an opinion on the acceptability of a specific use of a novel methodology in the context of research and development (5). This opinion is publically available on the EMA website and based on the assessment of data submitted to the EMA. The CHMP can also issue an advice on protocols and methods that are intended to develop a novel method with the aim of moving towards qualification (5). Additionally, the CHMP can provide medicine developers advice on study protocols, including endpoint selection, of a medicinal product with the aim of marketing approval (6). Both qualification advices (QAs) and scientific advices (SAs) are confidential and only provided to applicants.

The aim of the current study was to evaluate the scope and types of RMTs that are currently intended to be used in clinical trials for supporting/submitting application for obtaining marketing authorization (registration trials). Furthermore, we systematically collected the main recommendations and attention points of the CHMP concerning endpoints that are generated by mHealth technologies by evaluating the QOs, QAs, and SAs of the CHMP between 2013 and 2019 that covered RMTs.

METHODS

SAs, QAs, and QOs of the CHMP of the EMA were evaluated on the use of RMTs in registration trials that were issued between 2013, and 2019. QAs and QOs that assessed novel endpoints or improved established endpoints measured by mHealth technologies that can be used in a remote setting were included in our study. Likewise, SAs that covered studies using endpoints measured by RMTs were eligible for our study (inclusion criteria). We excluded advices and opinions that covered technologies that were solely used for the following: to document questionnaires and patient-reported outcome measures, for the delivery or administration of medicinal products, in animal studies or other preclinical studies, for therapeutic purposes, and non-electronic devices (exclusion criteria). In case more than one SA covered the same medicinal product and indication, only the first advice was included in our study.

QOs on novel methodologies for medicine development were accessed through the EMA website (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development) and QAs and SAs through the internal EMA database that contains these confidential documents. First, we identified potentially relevant documents in this database using the search terms "device" and "electronic." Next, we additionally searched the database using the following search terms that were based on findings of the first step: actimeter, actigraphy, actimetry, wearable, accelerometer, GPS, smartphone, and six specific names of commercial RMTs. All QAs and SAs that were identified using these search terms were carefully read to determine whether or not they met the inclusion and exclusion criteria. Likewise, only QOs that met the inclusion and exclusion criteria were included.

From the QOs and QAs, we extracted the following information: the device used and novel outcome measure(s), date, and main recommendations of the CHMP. Likewise,

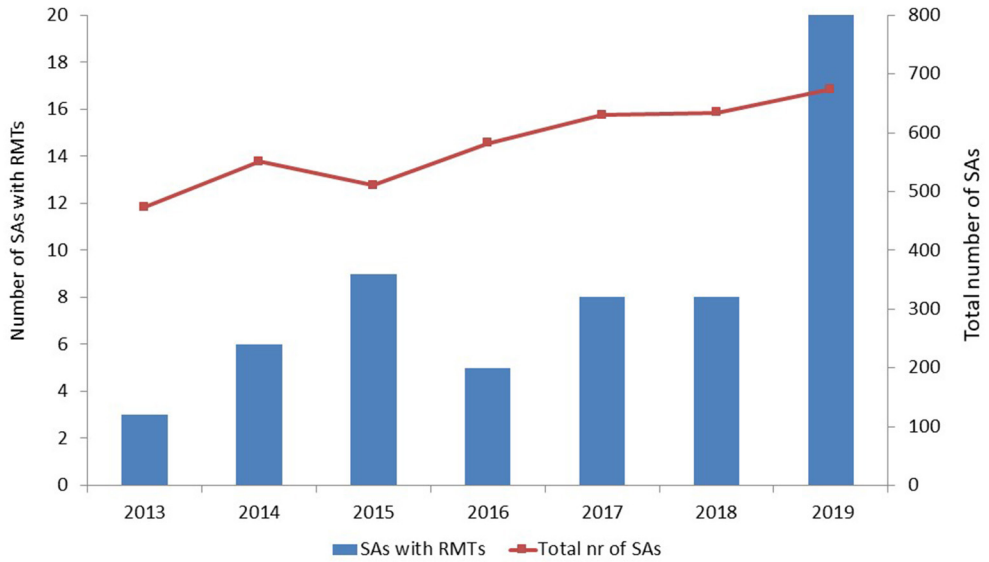


FIGURE 1 | Number of scientific advices that included remote monitoring technologies and total number of scientific advices per year. SAs, scientific advices; RMTs, remote monitoring technologies.

we collected information on the device(s) used and outcome measure(s), date, type of endpoint(s) (primary, secondary, or exploratory), and main recommendations of the CHMP of the SAs. In case an endpoint was proposed by the applicant as a primary (or secondary) endpoint, but this was not endorsed by the CHMP, the opinion of the CHMP was adopted. Since both QAs and SAs are confidential, we could not provide any information that could lead back to a specific medicinal product (SAs) or a novel endpoint (QAs). Therefore, results from these documents are presented at an aggregated level. This approach was approved by the legal departments of the Dutch Medicines Evaluation Board (MEB) and EMA.

RESULTS

Two QOs [stride velocity 95th percentile in Duchenne muscular dystrophy (7) and proactive in COPD (8)], four QAs, and 59 SAs met our inclusion and exclusion criteria. The number of SAs that included RMTs tended to increase over time, especially in 2019; however, the total number of SAs that the EMA issued also increased over time (**Figure 1**).

In a majority of the 59 SAs, accelerometers were proposed ($n = 31$) to monitor different activity and/or sleep parameters (**Table 1**). Other common devices included remote electronic peak flow, glucose, blood pressure, and heart rhythm measurement devices. In six QAs, mobile applications (apps) were considered for outcome measurement. These included apps to perform active tests ($n = 2$) and more complex mobile apps that combined both active and passive monitoring ($n = 4$). In a majority of cases, these mobile apps were proposed for measuring disease activity in neurologic or psychiatric disease areas ($n = 5$).

Subsequently, we determined for what type of endpoints the RMTs were proposed in the SAs. The majority of RMTs were proposed as secondary or exploratory endpoints (**Figure 2**). Furthermore, in 12 SAs, it was not entirely clear for what type of endpoint the applicant intended to use the outcome measure. In the majority of these cases, there was no clear distinction made between secondary or exploratory endpoints. In eight SAs, the measurement was accepted by the CHMP as a primary or co-primary endpoint. Furthermore, in one SA, the RMT was not endorsed by the CHMP, and an alternative method to assess the outcome measure was proposed. Lastly, in one SA, the RMT was intended to be used for outcome measurement in an explorative natural history study. Safety measures included the following: ketone or hypoglycemia measurement ($n = 2$) and remote measurement of QT/QTc intervals or detection of arrhythmias ($n = 3$).

The main questions and recommendations of the CHMP for applicants of the QOs, QAs, and SAs are summarized in **Table 2**. The main questions and concerns of the CHMP were related to (1) the relevance of the (novel) outcome measure for the disease; (2) validation of the novel outcome measure; (3) precision, accuracy, sensitivity, and specificity of the novel endpoint; (4) compliance and handling of missing values; (5) sampling interval; and (6) data handling, accessibility, and privacy. In case the novel endpoint was expected to be an improved measure compared to the established outcome measure, not all recommendations of **Table 2** do fully apply. This was acknowledged by the CHMP. Additionally, applicants frequently asked the CHMP questions relating to the medical device regulation. However, this is not the remit of the CHMP, and applicants were advised to direct these questions to a notified body.

Some attention points of the CHMP will be illustrated. Applicants should provide information on compliance with

TABLE 1 | Overview of remote monitoring devices and outcome measures of the scientific advices.

Device	Type of outcome measure(s)	Number of scientific advices
Accelerometer*	Activity measure(s)	17
Accelerometer*	Sleep measure(s)	9
Accelerometer*	Activity and sleep measures	3
Accelerometer*	Sleep and itch patterns	2
Electronic peak flow meter	Different lung function measures	3
Blood pressure measurement device	Different blood pressure measures	3
Heart rhythm and ECG measurement devices	ECG parameters and/or arrhythmias	3
(Continuous) glucose monitoring device	Glucose control measures#	6
Cough monitor	Cough frequency	3
App (active tests)	Measures of cognitive function	2
App (active and passive monitoring)	Different measures of disease activity	4
Not specified^		4

Different types of devices that contain accelerometers were combined, #including ketone measurement (n = 1), ^included are the following technologies: actigraphy without specification of outcome of interest (n = 1), "mobile wearable device to measure physiological parameters" (n = 1), "mobile technology (app) and telemedicine capabilities" to perform virtual clinics and monitor safety and efficacy (n = 1), and technology to conduct study visits remotely (n = 1).

a technology and handling of missing values. Selective non-compliance might be an issue, especially if compliance is relatively low. In case of mobile applications for instance, patients may be less likely to perform active tests when they experience more symptoms. This might partly be prevented by instructing the patient to perform the test every day at the same time, and electronic reminders such as alarms. Furthermore, the use of medication trackers might be relevant, especially for conditions with clear on/off states such as Parkinson's disease where patients can experience much more symptoms when levodopa starts to wear off (category D: compliance).

For many novel endpoints generated by RMTs, sampling intervals need to be determined. In case of "stride velocity 95th percentile in Duchenne muscular dystrophy measured by a wearable and valid device," a recording period of 180 h per month was chosen [QO, (7)]. Argumentations were that (A) variability decreased up to a plateau after this recording period, (B) this period seemed short enough to be used as a baseline measurement and long enough to cover week-to-week variations in activity, (C) disease progression is not expected during this period, and (D) patient burden was not considered to be too strenuous (category E: sampling interval). This sampling interval was endorsed by the CHMP.

Since RMT data need to be stored and transported to the research site, data handling and privacy issues need to be addressed. In case of the QO of stride velocity 95th percentile in Duchenne muscular dystrophy, a risk analysis was conducted by the applicant and considered acceptable by the CHMP. One reason that privacy was not a big concern in this QO was that the data recorded were only motion sensors of wrist and ankles, and no private information such as GPS location or name and address could be retrieved from the wearable device and system measures (category F: privacy and data handling).

DISCUSSION

The present study shows that the use of RMTs in a regulatory context is still relatively rare, and the majority of RMTs were proposed for measurement of secondary or exploratory endpoints. The most commonly used RMTs are accelerometers that can evaluate both measures of activity and sleep. Other RMTs include mobile apps that track disease activity, electronic peak flow meters, continuous glucose monitoring, blood pressure and heart rhythm monitoring, and remote cough measurement devices. Most recommendations of the CHMP apply to all novel endpoints and are not specific for mHealth technologies, such as relevance of the novel endpoint for the indication of interest; validation with current golden standard and legacy endpoints; and sensitivity, specificity, accuracy, and precision of the novel endpoint. Recommendations that are more specific for RMTs include good compliance and acceptability of the novel technology and guarantee of optimal data security and privacy.

Currently, comprehensive guidance on the development of novel endpoints generated by mHealth technologies is lacking in Europe. However, the EMA recently published a Q&A on the qualification of digital technologies (4), and globally, several other initiatives in this field exist. The CTTI, a public–private partnership between the FDA, academics, and pharma companies, was created in 2007 to develop practices that will increase the quality and efficiency of clinical trials. The CTTI project "Novel Endpoints" issued recommendations for the development of a novel endpoint generated by mobile technologies, including a stepwise approach for the development process (3, 9). This approach consists of a first section that describes a pathway for selection of outcome assessment, mobile technology, and patient population as well as a second section that addresses specific development steps for a mobile technology-derived outcome assessment into an endpoint for regulatory clinical trials (9).

The importance of most of the steps of the CTTI approach is also stressed by the CHMP. One exception is the CTTI recommendation to develop a user manual. This was not explicitly recommended by the CHMP in the QOs and QAs we evaluated, possibly because this was already provided by most applicants. Furthermore, in its approach, the CTTI emphasizes the importance of patients' and caregivers' insights in the selection process of meaningful health aspects, concepts of interests, and specific measurements. Although the CHMP specifically requested information on the correlation of novel endpoints with outcome measures such as quality of life and patient-reported outcome measures (PROMs) in many advices and opinions, this specific point of attention was made less clear by the CHMP in the documents we evaluated regarding RMTs. In general, in the assessment of novel endpoints generated by

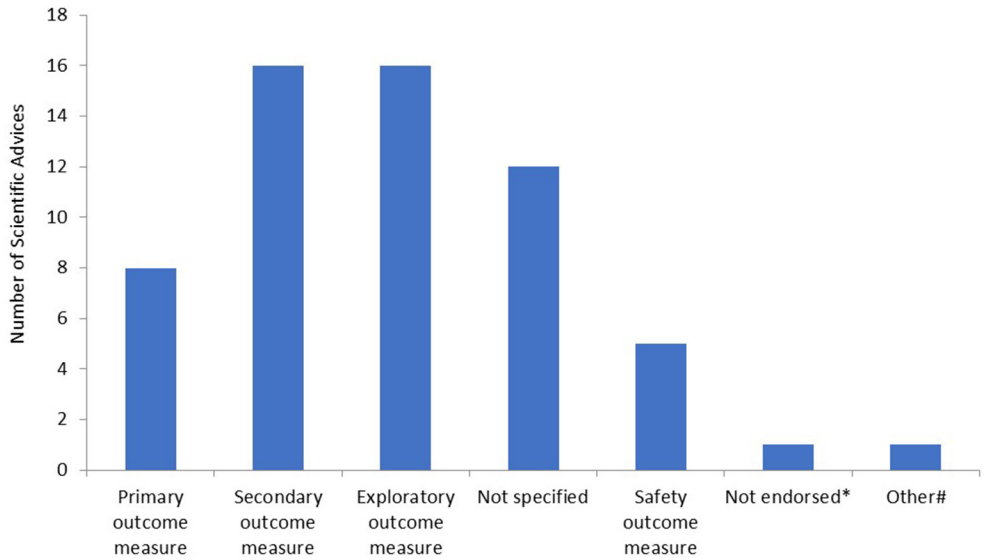


FIGURE 2 | Type of endpoints as measured by remote monitoring technologies. *In this scientific advice (SA), the remote monitoring technology (RMT) was not endorsed by the Committee for Medicinal Products for Human Use (CHMP) and another method for outcome measurement was proposed by the CHMP; #in this SA, the RMT was used in an explorative natural history study.

RMTs, the CHMP focused on validation of the new outcome measure with a golden standard or legacy measure that are usually part of the CHMP guideline for the corresponding disease. Although patient organizations and individual patients currently participate in several boards, committees, and working parties of the EMA, including SA and *ad-hoc* expert groups (10), patients' views on selection of novel endpoints and technologies could get a more prominent place in the EMA's procedures.

Many organizations underline the importance of pre-competitive collaboration, for instance for the development of industry-wide standards for the collection and reporting of data captured by mobile technologies and algorithms used to convert the data into medically meaningful endpoints (2, 9). Several of these collaborations exist (11–14), including different Innovative Medicines Initiative (IMI) projects such as IMI WEB-RADR that developed a mobile app for adverse drug reaction reporting (15). The Duke-Margolis Center for Health Policy also recommends to create such collaborations in their mHealth action plan for real-world evidence generation that they released in collaboration with the FDA (2). They propose a learning mHealth research community, in which patient representatives, analytics tool companies, device and pharma industries, clinical societies and healthcare centers, researchers, payers, and regulators participate. In their plan, the mHealth research community should consist of four learning areas that focus on patient engagement, clinician engagement, methods and tools for using mHealth data, and defining fit-for-purpose.

In Europe, the HMA-EMA Joint Big Data Taskforce issued a subgroup report on social media and mHealth data (1). They recommended to bring relevant stakeholders together to promote the use of innovative mHealth technologies and facilitate learning of regulators on topics such as technological capability, data quality, and analytical methodologies for mHealth technologies. Next to this, they advised to liaise with medical device regulators to ensure effective regulation of mHealth devices. Furthermore, regulators could contribute to data quality by more proactively defining expectations, for instance by defining to what extent and type of validation is required for different types of mHealth data, and considering the need for specific regulatory guidance. Lastly, they recommended to explore how apps and mHealth devices might be used within pharmacovigilance and post-authorization research. Although this subgroup report was a good starting point, it did not provide specific guidance on the use of mHealth technologies in registration trials. Possibly, this might (partly) explain why our study shows that RMTs are infrequently used in the regulatory context up until 2019, despite recent technological developments.

As of June 2020, the EMA published a Q&A on the *Qualification of digital technology-based methodologies to support approval of medicinal products* (4). Although this document is not intended as comprehensive guidance, it provides some key recommendations for successful qualification. As expected, most points addressed in this Q&A were also identified by the evaluation of opinions and advices of our study, which were issued before this Q&A was available. However, some recommendations were not explicitly mentioned in our overview of the main recommendation of the CHMPA. These include (1) rationale to support the added benefit as compared to traditional methods; (2) evolution of the device throughout the validation program, what changes were made to the system, when, and their potential impact; and (3) ensuring the correct use of the technology by a best practice guide. Furthermore, the Q&A emphasizes the importance of "the context of use" as a critical reference point for regulatory assessment of any qualification

TABLE 2 | Main concerns and questions of the CHMP for the applicants.

Main recommendations
A. Relevance of the (novel) outcome measure as assessed by the remote monitoring technology
Is the outcome measure relevant for the disease of interest?
Does the device measure all aspects or symptoms of a specific disease?
Does the device measure all aspects of a specific function?
To what extent is the outcome measure only influenced by the disease activity of interest?
How does the outcome measure relate to the CHMP guideline of the corresponding disease?
In case of sensor data: to what extent is the body part to which the sensor is attached reflective of the symptoms of the disease or condition of interest?
B. Validation of the novel outcome measure as assessed by the remote monitoring technology
Is the outcome measure correlated with hard endpoints? (morbidity/mortality)
Is the outcome measure correlated with relevant outcome measures for patients? [Quality of life (QOL) and patient-reported outcome measures (PROMs)]
Is the outcome measure correlated with the established/golden standard clinical tests and/or PROMs of the disease of interest?
In case several established outcome measures exist that measure different symptoms or aspects of a disease: to what extent does the novel outcome correlate with all these different endpoints? (NB relevance of an outcome measure can depend on the intended treatment effect)
Is a change in the novel endpoint correlated with a change in final endpoints or (other) outcomes that matter to patients? (QOL or PROMs)
What is the external validity? In how many patients/persons has the device been tested?
Is the minimal clinically important change determined? If yes: is this studied prospectively?
Is the minimal clinically important change determined for the different diseases, subgroups and clinical stages of interest?
C. Precision, accuracy, sensitivity, and specificity
To what extent does the novel endpoint predict the established endpoint(s) with enough precision?
What is the internal validity? (same value in stable patients)
Are there systematic errors in measurements in specific subgroups? (e.g., overestimation of walking speed in more severe multiple sclerosis patients due to ataxia)
In case several outcome measures are available for a device: what outcome measure is chosen and why?
What is the effect of outliers and was this taken into account?
To what extent can the device check what the activity of the patient is during the measurement? If relevant: how is this issue handled?
Is the outcome measure sensitive enough to distinguish relevant subgroups?
Technical correctness: to what extent is the device capable of measuring a change that is clinically relevant?
D. Compliance and handling of missing values
What is the compliance?
Is the compliance stable during follow-up?
Is selective non-compliance an issue? (e.g., a patient does not perform tests or wears a device during periods of increased symptomatology)
What measures are taken to prevent (selective) missing values?
Is compliance actively stimulated? (e.g., by the use of alarms, phone calls, etc.)
How are missing data handled?
In case of an active test: is the test performed every day at the same time? Is a medication tracker used? (this can be of relevance in case of clear on/off states such as in Parkinson's disease)
Wat is the tolerability and acceptability of the technology for patients?
E. Sampling interval
Is the sampling interval long enough to take day-to-day variation into account?
Is the sampling interval per measurement short enough that no clinical change is expected and optimal compliance is expected?
How is the sampling interval determined?
F. Privacy and data handling
How are data anonymized and protected?
Who has access to the data?
Is a risk analysis performed to guarantee optimal data security?

application. In this context, the impact of the use of different digital technologies (e.g., bring your own device) should be discussed, and a risk management plan should be provided, including for example information on interference with other applications on the device, effect of upgrades, etc. Lastly, the Q&A contains some practical recommendations such as early interaction with EMA during the development process.

To the best of our knowledge, the current study is the first study that systematically evaluates the opinions and recommendations of the CHMP on the use of RMTs in QOs, QAs, and SAs. Next to this, our study provides insight in the current use of RMTs in a regulatory context. Limitations of our study are that we focused on RMTs that measure efficacy and safety endpoints. We excluded advices and opinions that covered technologies that were solely used to measure compliance and devices that were only used as e-diaries or questionnaires, even if these devices were used to assess efficacy or safety outcomes. Furthermore, detailed recommendations for validation of composite scores, for instance in case of mobile apps combining passive and active tests, were considered beyond the scope of this research. Next, we could have erroneously excluded relevant advices and opinions in case they did not match our search terms. However, this seems less likely given our extended second search round using search terms based on the results of our first search. Lastly, despite our detailed evaluation, we could have overlooked some recommendations or opinions of the

CHMP in the QOs, QAs, and SAs, since this part of our research was qualitative by nature.

In conclusion, our study shows that, despite the current pace of technological innovation, the use of RMTs in the regulatory context is still relatively limited. In the absence of formal European guidance on the use of mHealth technologies, our study provides insight in the main recommendations and attention points of the CHMP. These include relevance of the novel endpoint for the indication of interest; validation with current golden standard and legacy endpoints, including those endpoints that matter most to patients; sensitivity, specificity, accuracy, and precision of the novel technology; good compliance and acceptability; and guarantee of optimal data security, and privacy. The development of clear guidance for the use of mHealth technologies in registration trials might promote the development of novel improved endpoints and improve ultimately data quality and regulatory decision making.

DATA AVAILABILITY STATEMENT

The data presented in this article are not readily available because SAs and QAs contain confidential information that cannot be shared publicly. Requests to access the datasets should be directed to Anna M. G. Pasmooij, am.pasmooij@cbg-meb.nl.

AUTHOR CONTRIBUTIONS

MD collected the data and drafted the work. MD and AP were involved in the interpretation of the data. PS and AP revised the manuscript critically. All authors contributed substantially to the conception and design of the work and read and approved the final version of the manuscript.

FUNDING

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement no. 806999 (Remote Assessment of Disease and Relapse—Alzheimer's Disease). This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and European Commission and the European Federation of Pharmaceutical Industries and Associations (http://www.imi.europa.eu/).

ACKNOWLEDGMENTS

We thank Dr. P. G. M. Mol and Dr. J. H. Ovelgönne, both members of the Scientific Advice Working Party of the EMA, for their practical help with and instructions for searching the EMA database and interpretation of our study results.

REFERENCES

1. HMA/EMA Big Data Task Force, Donegan K, Ovelgönne H, Flores G, Fuglerud P, Georgescu A. *Social Media and m-health Data, Subgroup Report* (2019). Available online at: https://www.ema.europa.eu/en/documents/report/social-media-m-health-data-subgroup-report_en.pdf (accessed April 28, 2020).
2. Duke Margolis Center for Health Policy, Atreja A, Bates D, Clancy S, Daniel G, Doerr M, et al. *Mobilizing mhealth Innovation for Real-World Evidence Generation* (2017). Available online at: https://healthpolicydukeedu/sites/default/files/atoms/files/mobilizing_mhealth_innovation_for_real-world_evidence_generationpdf (accessed April 28, 2020).
3. Clinical Trials Transformation Innitiative (CTTI). *Developing Novel Endpoints Generated by Mobile Technologies for Use in Clinical Trials* (2017). Available online at: https://www.ctti-clinicaltrials.org/projects/novel-endpoints (accessed April 28, 2020).
4. European Medicines Agency. *Human Medicines Division*. Available online at: https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf (accessed October 19, 2020).
5. European Medicines Agency. *Opinions and Letters of Support on the Qualification of Novel Methodologies for Medicine Development*. Available online at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development (accessed April 28, 2020).
6. European Medicines Agency. *Scientific Advice and Protocol Assistance*. Available online at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance (accessed April 28, 2020).
7. European Medicines Agency, Committee for Medicinal Products for Human Use. *Qualification Opinion on Stride Velocity 95th centile as a Secondary Endpoint in Duchenne Muscular Dystrophy Measured by a Valid and Suitable Wearable Device* (2019). Available online at: https://wwwemaeuropaeu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular-dystrophy_enpdf (accessed April 28, 2020).
8. European Medicines Agency, Committee for Medicinal Products for Human Use. *Qualification Opinion on Proactive in COPD* (2018). Available online at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-proactive-chronic-obstructive-pulmonary-disease-copd_en.pdf (accessed April 28, 2020).
9. Clinical Trials Transformation Innitiative (CTTI). *Steps for Novel Endpoint Development, with Suggested Approaches and Considerations* (2017). Available at: https://wwwctti-clinicaltrialsorg/files/detailedstepspdf (accessed April 28, 2020).
10. European Medicines Agency. Available online at: https://www.ema.europa.eu/en/partners-networks/patients-consumers/getting-involved (accessed April 28, 2020).
11. Gastfriend E, Lee B. *Pre-Competitive Collaboration in Pharma, an Overview Study* (2015). Available online at: https://futureoflife.org/data/documents/PreCompetitiveCollaborationInPharmaIndustry.pdf. (accessed April 28, 2020).
12. Innovative Medicines Innitiative. *Europe's Partnership for Health*. Avail.able online at: https://www.imi.europa.eu/ (accessed April 28, 2020).
13. Clinical trials transformation innitiative (CTTI). Available online at: https://www.ctti-clinicaltrials.org/ (accessed April 28, 2020).
14. Weninger S, Carrillo MC, Dunn B, Aisen PS, Bateman RJ, Kotz JD, et al. Collaboration for Alzheimer's prevention: principles to guide data and sample sharing in preclinical Alzheimer's disease trials. *Alzheimers Dement.* (2016) 12:631–2. doi: 10.1016/j.jalz.2016.04.001
15. Pierce CE, de Vries ST, Bodin-Parssinen S, Harmark L, Tregunno P, Lewis DJ, et al. Recommendations on the use of mobile applications for the collection and communication of pharmaceutical product safety information: lessons from IMI WEB-RADR. *Drug Saf.* (2019) 42:477–89. doi: 10.1007/s40264-019-00813-6

Disclaimer: The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees, working parties, or any

of the national agencies. This communication reflects the views of the RADAR-AD consortium and neither IMI nor the European Union are liable for any use that may be made of the information contained herein.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

REVIEW
published: 06 July 2021
doi: 10.3389/fmed.2021.688438

Scientific Advances in Diabetes: The Impact of the Innovative Medicines Initiative

Maria de Fátima Brito [1], Carla Torre [1,2] and Beatriz Silva-Lima [1,2]*

[1] Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal, [2] Laboratory of Systems Integration Pharmacology, Clinical & Regulatory Science–Research Institute for Medicines (iMED.ULisboa), Lisbon, Portugal

Diabetes Mellitus is one of the World Health Organization's priority diseases under research by the first and second programmes of Innovative Medicines Initiative, with the acronyms IMI1 and IMI2, respectively. Up to October of 2019, 13 projects were funded by IMI for Diabetes & Metabolic disorders, namely SUMMIT, IMIDIA, DIRECT, StemBANCC, EMIF, EBiSC, INNODIA, RHAPSODY, BEAT-DKD, LITMUS, Hypo-RESOLVE, IM2PACT, and CARDIATEAM. In general, a total of €447 249 438 was spent by IMI in the area of Diabetes. In order to prompt a better integration of achievements between the different projects, we perform a literature review and used three data sources, namely the official project's websites, the contact with the project's coordinators and co-coordinator, and the CORDIS database. From the 662 citations identified, 185 were included. The data collected were integrated into the objectives proposed for the four IMI2 program research axes: (1) target and biomarker identification, (2) innovative clinical trials paradigms, (3) innovative medicines, and (4) patient-tailored adherence programmes. The IMI funded projects identified new biomarkers, medical and research tools, determinants of inter-individual variability, relevant pathways, clinical trial designs, clinical endpoints, therapeutic targets and concepts, pharmacologic agents, large-scale production strategies, and patient-centered predictive models for diabetes and its complications. Taking into account the scientific data produced, we provided a joint vision with strategies for integrating personalized medicine into healthcare practice. The major limitations of this article were the large gap of data in the libraries on the official project websites and even the Cordis database was not complete and up to date.

Keywords: innovative medicines initiative, diabetes, complications of diabetes, personalized medicine, type 2 diabetes, type 1 diabetes

OPEN ACCESS

Edited by:
Hilde Stevens,
Université libre de Bruxelles, Belgium

Reviewed by:
Frits Lekkerkerker,
Consultant, Amsterdam, Netherlands
Jordi Llinares Garcia,
European Medicines Agency, Netherlands

****Correspondence:***
Maria de Fátima Brito
maria.fatima.brito@campus.ul.pt

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *30 March 2021*
Accepted: *02 June 2021*
Published: *06 July 2021*

Citation:
Brito MdF, Torre C and Silva-Lima B (2021) Scientific Advances in Diabetes: The Impact of the Innovative Medicines Initiative. Front. Med. 8:688438. doi: 10.3389/fmed.2021.688438

INTRODUCTION

Innovative Medicines Initiative (IMI) is a unique pan-European public and private partnership that pioneered large-scale open collaborations between large pharmaceutical companies, small and medium-sized enterprises, public authorities (including regulators), organizations of patients, academia, and clinical centers to throw bottlenecks in research and development (R&D) of new effective and safer medicines (1).

To implement the Innovative Medicines Initiative, the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) hold joint responsibility for creating and operating a new non-profit international organization (1).

IMI aims to accelerate the discovery and development of more effective vaccines, medicines, and treatments with fewer side-effects, especially in areas where there is an unmet medical or social need. IMI intends to implement patient centered projects, prompting the patient access to innovative pharmaceutical options (1, 2). This initiative provide socio-economic benefits and contribute to the health of European citizens, minimize duplication of work at different organizations, increase competitiveness, and help to establish Europe as the most attractive and competitive site for innovation (1, 2).

The first programme of IMI (IMI1) was created by Council Regulation (EC) n.° 73/2008, of 20th December 2007. The overall aim was to support pre-competitive pharmaceutical research and development, through the funding of innovative patient-centered projects for the research of European health priorities defined by the World Health Organization (WHO) (3). IMI1 programme was based on four strategic interdependent areas (Four-pillars) namely Safety, Efficacy, Knowledge Management, and Education and Training (1). The vision of this programme consisted on the creation of new scientific knowledge and capabilities/techniques to support the ability to identify a lack of efficacy or safety quickly in all stages of the medicine development process, even when a potential medicine has promising pre-clinical data (1). In addition, IMI1 programme intended to support the benefit-risk assessment conducted by the regulatory authorities (1, 2).

For this initiative, the budget committed was €2 billion (2, 4). During the execution period of IMI1 programme (2008 to 2013), eleven calls for proposals were released, which resulted in 59 funded-projects (4, 5).

The success of the IMI1 programme prompted the European Commission and the European Federation of Pharmaceutical Industries and Associations to take the commencing of initiating a second IMI programme (IMI2) under the Horizon 2020 vision of "improve the health and well-being of populations, reduce health inequalities, and ensure sustainable people-centered health systems" (5). Innovative Medicines Initiative 2 Joint Undertaking was established by Regulation (EU) n.° 557/2014, 6th of May (6). The major research axes recognized for IMI2 were: target & biomarker identification, innovative clinical trial paradigms, innovative medicines, and patient tailored adherence programmes (5). This programme ran from 2014 to 2020 and the budget committed was up to €3.276 billion, half funded by the European Comission and the other part from EFPIA.

Diabetes mellitus (DM) is one of the eleven priority diseases addressed by IMI1 and IMI2 programmes in the Strategic Reseach Agenda. This is a chronic metabolic disorder characterized by a defined phenotype (hyperglycemia accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids, and proteins), triggered by either lack of insulin secretion or decreased sensitivity of the tissues to insulin (7–9). Worldwide, a majority of diabetic patients (80–90%) have type 2 diabetes (T2D) and 5–10% type 1 diabetes (T1D) (8).

In 2014, WHO estimated that the prevalence of diabetes could reach more than 20% of the world's population within the next 20 years (8, 10, 11). Besides, the diabetes-associated mortality rate has been increasing, being the seventh leading cause of death in 2016 (12), and the disease and its acute and chronic complications represent a major economic burden on the global healthcare system and the wider global economy (5). For all the factors, previously presented, WHO considered this disease as the pandemic of the 21st century (8).

With the purpose of slowing the increasing prevalence, decreasing the mortality rate and diminishing the economic burden of diabetes and its related complications, IMI focused on projects aimed at understanding T1D and T2D, developing new precision medicines, identifying better patient-focused outcome measures for diagnosis, treatment selection and prognosis of T1D, T2D, and complications of diabetes, as well as promoting better lifestyle management and adherence to prescribed medicines (1, 5).

IMI1 programme funded six projects in the Diabetes & Metabolic disorders field, namely: Surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools (SUMMIT), Improving beta-cell function and identification of diagnostic biomarkers for treatment monitoring in diabetes (IMIDIA), Diabetes research on patient stratification (DIRECT), Stem cells for biological assays of novel medicines and predictive toxicology (StemBANCC), European Medical Information Framework (EMIF), and European Bank for induced pluripotent Stem Cells (EBiSC).

In IMI2 programme, until October of 2019, seven projects were supported in the area of Diabetes & metabolic disorders (13). These projects were: Translational approaches to disease modifying therapy of type 1 diabetes: an innovative approach toward understanding and arresting type 1 diabetes (INNODIA), Assessing risk and progression of prediabetes and type 2 diabetes to enable disease modification (RHAPSODY), Biomarker enterprise to attack DKD (BEAT-DKD), Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS), Hypoglycaemia–redefining solutions for better lives (Hypo-RESOLVE), Investigating mechanisms and models predictive of accessibility of therapeutics into the brain (IM2PACT), and Cardiomyopathy in type 2 diabetes mellitus (CARDIATEAM).

Of the 13 projects, one was targeted to type 1 diabetes—INNODIA, three to type 2 diabetes—DIRECT, EMIF, and RHAPSODY, four to complications of diabetes—SUMMIT, BEAT-DKD, LITMUS, Hypo-RESOLVE, and CARDIATEAM, and the remaining four were scientific-oriented—StemBANCC, EBiSC, IMIDIA, and IMI2PACT. A more detailed description of the projects and its objectives is available in **Supplementary Material** section.

A total of €447.249.438 was mobilized for Diabetes (€253.865.866 from IMI1 and €193.383.572 from IMI2), however there has not been a systematization of scientific production by the IMI-funded projects.

The purpose of this literature review was to summarize the project results of IMI1 and IMI2 programmes into the major research axes of IMI2 programme and propose a joint vision model including the data collected into two inter-dependent paths, one scientific-oriented and the other medical-oriented.

MATERIALS AND METHODS

The data sources used in this review were the IMI website, the official project websites, contact with the project coordinators

TABLE 1 | Summary of sources and publications included in this study.

Projects	Articles obtained by contact via e-mail	Publications retrieved from the project's website	Articles collected on CORDIS database
SUMMIT	–	52	42
IMIDIA	–	13	16
DIRECT	25	NA	NA
StemBANCC	–	91	31
EMIF	–	47	0
EBiSC	–	6	9
INNODIA	–	47	32
RHAPSODY	–	20	19
BEAT-DKD	–	52	38
LITMUS	–	0	0
Hypo- RESOLVE	0	0	0
IMI2PACT	–	0	0
CARDIATEAM	–	0	0

NA, Not applicable.

and co-coordinators, and the CORDIS (The Community Research and Development Information Service) database. From IMI website it was collected the project's start and end date, the grant agreement number, the contributions, and the coordinators and co-coordinators' e-mail addresses. The aim of each project was retrieved from its official website. The sources of the publications were the project's official website, CORDIS database, and the contact via e-mail with the coordinators and co-coordinators (**Table 1**).

The contacts with the coordinators and co-coordinators were conducted in January of 2019 and for non-respondents, a recall in February of 2019. This step was performed for all projects.

The literature research on the project's websites and the CORDIS databases was conducted from February 2019 to October 2019. In October 2019, a new consultation was conducted on the IMI website, and the new funded projects (IMI2PACT and CARDIATEAM) were included.

For SUMMIT's project, a total of 98 citations were screened, 52 from the SUMMIT's website and 46 from the CORDIS database. A total of 67 references were excluded: (i) duplicates−29, (ii) book chapters−2, (iii) not access to the full text−7, (iv) the publication's objective was not related to diabetes mellitus or its complications−9, and (v) the publication's achievements did not allow to induce a scientific advance in Diabetes field (e.g., state of the art, outdated information, the article's data don't address an objective of the IMI2 programme)−20. For this project, a total of 31 articles were included.

For IMIDIA's project, a total of 29 citations were screened, 13 from the IMIDIA's website and 12 from CORDIS database. A total of 11 references were excluded: (i) duplicates−5, (ii) book chapters−1, (iii) the publication's objective was not related with diabetes mellitus or its complications−3, and (iv) the publication's achievements did not allow to induce a scientific advance in Diabetes field (e.g., state of the art, outdated information, the article's data don't address an objective of the IMI2 programme)−2. For this project, a total of 18 articles were included.

For DIRECT's project, a total of 25 citations were screened on the list of publications sent by the project coordinator. Since this list is not available online (either on the project's website or on CORDIS database), we present it in the **Supplementary Material** section. A total of nine references were excluded: (i) duplicates−1, (ii) not access to the full text−2, and (iii) the publication's achievements did not allow to induce a scientific advance in Diabetes field (e.g., state of the art, outdated information, the article's data don't address an objective of the IMI2 programme)−6. For this project, a total of 16 articles were included.

For StemBANCC's project, a total of 122 citations were screened, 91 from the StemBANCC's website and 31 from CORDIS database. A total of 103 references were excluded: (i) duplicates−30, (ii) book chapters−1, (iii) the publication's objective was not related to diabetes mellitus or its complications−71, and (iv) the publication's achievements did not allow to induce a scientific advance in Diabetes field (e.g., state of the art, outdated information, the article's data don't address an objective of the IMI2 programme)−1. For this project, a total of 19 articles were included.

For EMIF's project, a total of 165 citations were screened, all from the EMIF's website. A total of 136 references were excluded: (i) duplicates−1, (ii) article's exclusion criterion was the presence of diabetes−1, (iii) the publication's objective was not related with diabetes mellitus or its complications−120, and (iv) the publication's achievements did not allow to induce a scientific advance in Diabetes field (e.g., state of the art, outdated information, the article's data don't address an objective of the IMI2 programme)−14. For this project, a total of 29 articles were included.

For EBiSC's project, a total of 15 citations were screened, six from the EBiSC's website and 9 from CORDIS database. A total of 14 references were excluded: (i) the publication's objective was not related to diabetes mellitus or its complications (e.g., state of the art, outdated information, the article's data don't address an objective of the IMI2 programme)−14. For this project, a total of one article was included.

For INNODIA's project, a total of 79 citations were screened, 47 from the INNODIA's website and 32 from CORDIS database. A total of 34 references were excluded: (i) duplicates−32, (ii) not access to the full text−1, and (iii) the publication's achievements did not allow to induce a scientific advance in Diabetes field (e.g., state of the art, outdated information, the article's data don't address an objective of the IMI2 programme)−11. For this project, a total of 35 articles were included.

For RHAPSODY's project, a total of 39 citations were screened, 20 from the RHAPSODY's website and 19 from CORDIS database. A total of 28 references were excluded: (i) duplicates−21, (ii) book chapters−1, and (iii) the publication's achievements did not allow to induce a scientific advance in Diabetes field (e.g., state of the art, outdated information, the article's data don't address an objective of the IMI2 programme)−6. For this project, a total of 11 articles were included.

For BEAT-DKD's project, a total of 90 citations were screened, 52 from the BEAT-DKD's website and 38 from CORDIS database. A total of 65 references were excluded: (i) duplicates—40, (ii) the publication's objective was not related to diabetes mellitus or its complications—10, and (iii) the publication's achievements did not allow to induce a scientific advance in Diabetes field (e.g., state of the art, outdated information, the article's data don't address an objective of the IMI2 programme)—15.

No results were identified in LITMUS, Hypo-RESOLVE, IMI2PACT, and CARDIATEAM projects.

The search and screening processes are summarized in **Figure 1**.

The results gathered in the literature review were integrated into the axes presented by the IMI2 programme, namely target & biomarker identification, innovative clinical trials paradigms, innovative medicines, and patient-tailored adherence programmes.

The data collected was organized according to the objectives established for each axis by the Strategic Research Agenda (SRA).

RESULTS

In Target & Biomarker identification axis, from the 10 objectives outlined in SRA, those achieved were (1) identify and validate biological markers, tools and assays, (2) determinants of inter-individual variability, (3) understand the molecular mechanisms underlying the disease, (4) develop a platform of pre-clinical assays, and (5) develop systems models.

For the "innovative clinical trial paradigms" axis, the data applied two of the twelve objectives defined in SRA, especially (1) utilize innovative endpoints, trial designs, simulation and analytical approaches to devise new clinical trial paradigms and (2) develop innovative clinical endpoints.

In the innovative medicines axis, from the eleven objectives in SRA, those with results were: (1) identify new or alternative therapeutic concepts (targets) for treatment and prevention of disease, (2) develop novel therapeutic agents and disease prevention strategies, and (3) as implement new approaches for the development and production of biopharmaceuticals and tissue engineering.

Lastly, from the seven objectives in SRA, the data collected for maximizing patient-tailored adherence programmes address only one goal, namely develop patient-centered predictive models.

In short, the outline of the projects with results in the research axes of the IMI2 programme, namely target & biomarker identification, innovative clinical trials paradigms, innovative medicines, and patient-tailored adherence programmes, is displayed in **Figure 2**.

No outputs were identified in LITMUS, Hypo-RESOLVE, IMI2PACT, and CARDIATEAM projects, as these were starting close to or during the literature search process.

Due to the quantity and diversity of data collected, we summarized the results obtained by each IMI funded-project in figures that are presented in **Supplementary Material** section.

A wide range of biomarkers have been identified for the onset of type 1 diabetes (14–24) by INNODIA; for risk prediction (14, 15, 17–21) and identification of patients at high-risk of type 2 diabetes (25) by SUMMIT, IMIDIA, DIRECT, and EMIF; for pancreatic β-cells function and protection by RHAPSODY (26, 27) and INNODIA (14, 16, 22–24); for hyperglycemia by RHAPSODY (28); for protection, prediction, initiation, progression, patient stratification, and medicine efficacy of diabetic kidney disease (DKD) (29, 30) by SUMMIT and BEAT-DKD (31–39); for development of cardiovascular disease (CVD) by SUMMIT (30, 40, 41); and for the development of diabetic retinopathy (DR) by SUMMIT (30, 42, 43).

Additionally, several novel tools were identified for diabetes, T1D, T2D, diabetic complications, and genetic research. The tools for diabetes intended to diagnose and monitoring disease progression [IMIDIA (44–49), DIRECT (50), and RHAPSODY (51)]. The tools designed for T1D were focused on monitor β-cell function, screen individuals at high risk, and select the more benefic intervention [INNODIA (15, 52, 53)]. For T2D, a new test was proposed to follow-up patients' insulin treatment need [EMIF (54, 55)]. Regarding diabetic complications, new tools were developed to enable the detection of patients at high risk of developing CVD and DR [SUMMIT (30, 56, 57)]. At last, in genetic research area, new tools were validated for the identification of single nucleotide polymorphism [SUMMIT (58–61) and StemBANCC (62, 63)].

Concerning the novel determinants of inter-individual variability, SUMMIT (43, 60, 64–72), IMIDIA (46, 49, 73–76), DIRECT (50, 77–82), EMIF (83–89), INNODIA (22, 23, 90–93), and RHAPSODY (27, 28, 94, 95) proposed a significant number of genetic markers for predisposition, initiation, identification, and progression of diabetes and its complications. Additionally, SUMMIT and DIRECT verified the influence of genetic factors in patients' medicine-response (96–101), and BEAT-DKD identified a non-genetic inter-individual therapeutic variability factor, i.e., NT-proBNP levels (37, 102, 103). DIRECT also confirmed the influence of gut composition (99, 100), age of diagnosis (50), year of diagnosis (104), and BMI factors (105) on the onset of diabetes, and EMIF showed the association with other factors such as ethnicity and metabolic health on T2D risk and development of complications (106). Moreover, two models of patient stratification were proposed, one by INNODIA for glycemic control in patients with T1D (107) and another by RHAPSODY and BEAT-DKD related with the identification of the patient's risk level for certain diabetic complications (108).

Novel relevant pathways were proposed to understand β-cell development and function [by IMIDIA (109–113), StemBANCC (114–119), and RHAPSODY (27)], type 1 diabetes (by INNODIA (16, 20, 23, 120–125), type 2 diabetes [by DIRECT (50), EMIF (85, 126–130), and Rhapsody (131)], CVD [SUMMIT (30, 132) and INNODIA (133)], DKD [BEAT-DKD (32, 36, 134–138)], DR [SUMMIT (30, 42, 43)], endometrial cancer risk [EMIF (139)], dementia [EMIF (140)], non-alcoholic fatty liver disease [EMIF (54, 55, 141–143)], anorexia or bulimia [INNODIA (125)], and attention-deficit hyperactivity disorder [INNODIA (125)].

In terms of pre-clinical studies, StemBANCC (114, 144, 145), EBiSC (146, 147), and IMIDIA (45, 49) proposed innovative

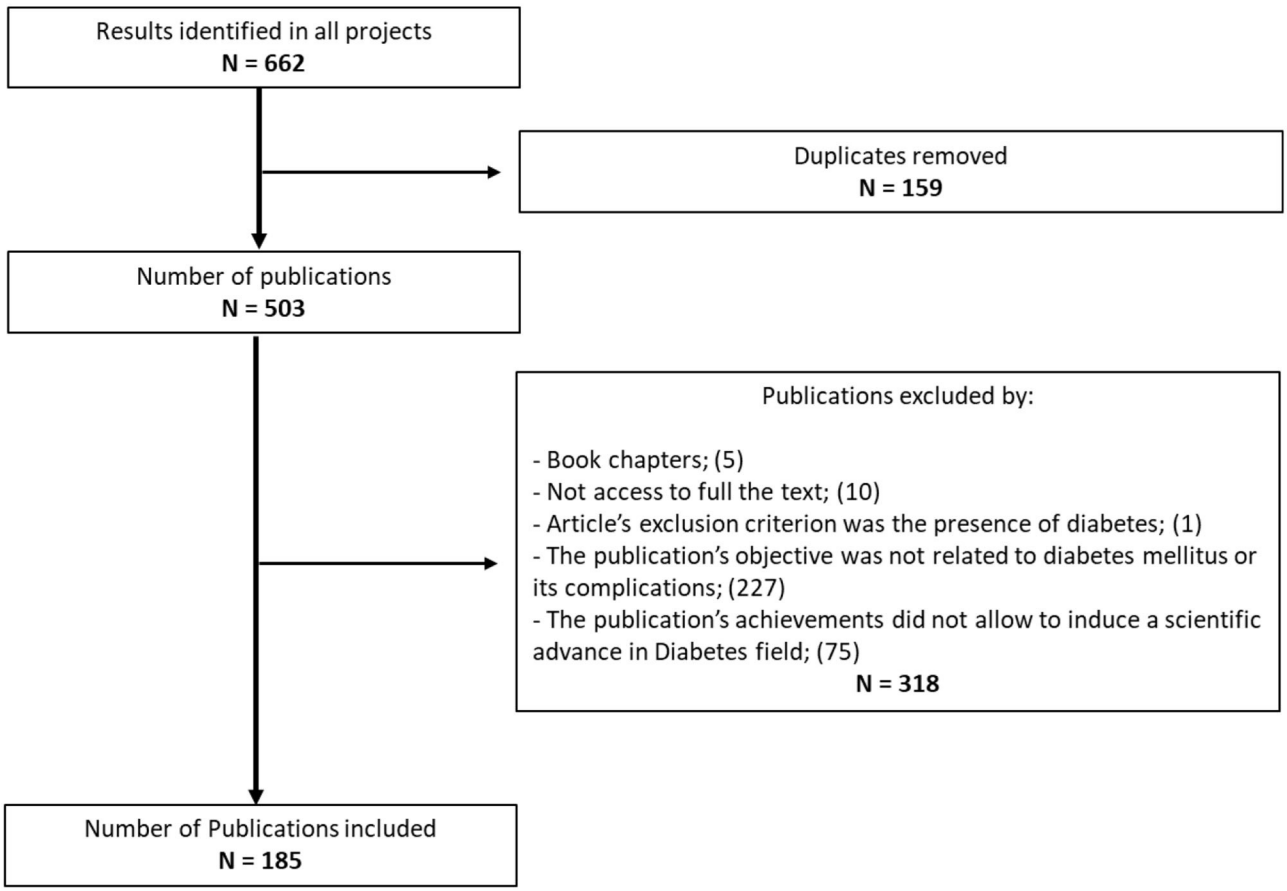


FIGURE 1 | Flowchart of literature search.

iPSCs lines derived from diabetes and created their own databases; StemBANCC, INNODIA and RHAPSODY developed three catalogs, namely β-cell' Bi-DOCS (148), HLA-I peptidome of β-cells (21) and cis-eQTLs for T2D (149); IMIDIA (44–49), StemBANCC (144, 150), and RHAPSODY (151) established several protocols to improve the reliability of laboratory studies; and SUMMIT (30, 152, 153) and IMIDIA (46) developed new specific animal models.

Regarding systems models, two new *in silico* models were generated by SUMMIT (30), one for clinical complications in T1D and the other for aspirin action. In addition, BEAT-DKD proposed three models associated with DKD, namely the *Drosophila* nephrocyte to reveal mechanisms of podocyte function and glomerular diseases (154), the systems biology to better prediction of patient's medicine- response (155), and an *in-silico* analysis to identify compounds reversing a set of renal age-associated genes associated with the disease's progression (32).

For clinical trials, two novel design models were proposed, one by DIRECT and a second by BEAT—DKD: the Genotype-based Recall (GBR) (156) and "umbrella" or "platform" trials (157, 158), respectively. Regarding the innovative clinical endpoints, DIRECT validated a prediction model for T2D–DIRECT-DETECT, which may be used in the selection process in clinical trials (159, 160).

New potential therapeutic targets were suggested for the treatment of accelerated atherosclerosis in diabetic patients (161) (SUMMIT), for treating glomerular disease in T2D patients (36, 135, 162–164) (SUMMIT), for T2D patients with obesity (165) (EMIF), for counteracting hyperglycemia in individuals with T2D (166) (IMIDIA), for prevent or reverse β-cell loss [IMIDIA (167), StemBANCC (114, 116, 168, 169) and INNODIA (14, 90, 120, 121, 170–172)], and for diabetes with a focus on the use of new concepts such as epitranscriptome-based therapy by RHAPSODY (173), StemBANCC (114–116, 168, 169, 174), EMIF (86), and RHAPSODY (173). In terms of novel pharmacologic agents for T2D, SUMMIT developed the clinical trials of Aleglitazar (175), RAAS inhibitors (176), and supported the use of low-dose aspirin for the secondary prevention of cerebro-cardiovascular events (177).

Furthermore, DIRECT demonstrated the cardio-metabolic benefit of metformin (178), BEAT-DKD supported the clinical efficacy of SGLT2 inhibitors and GLP1R agonists in diabetic patients with DKD (179, 180), and StemBANCC established

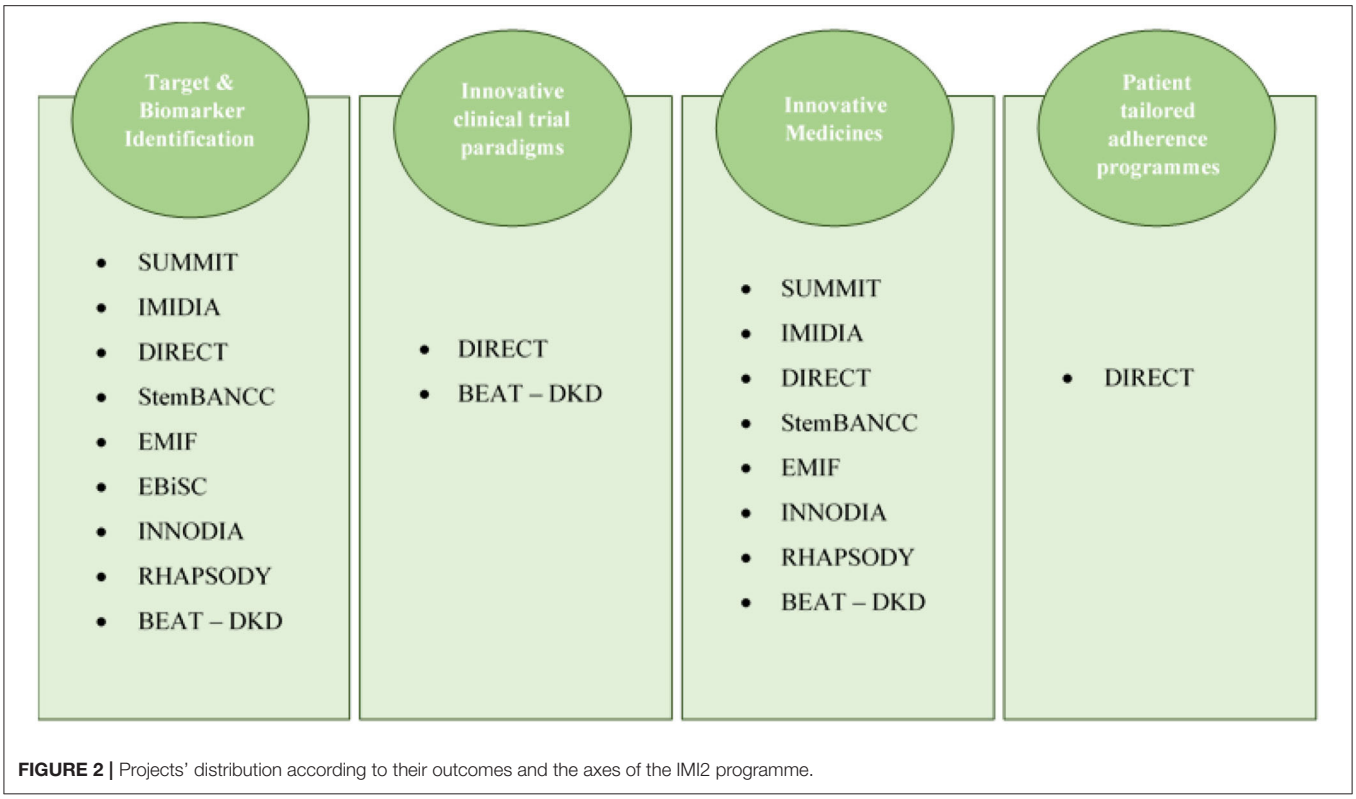


FIGURE 2 | Projects' distribution according to their outcomes and the axes of the IMI2 programme.

four different stem cell-based replacement treatments (181–183). For large-scale production, StemBANCC demonstrated that the continuous peristaltic pump-based circulation technology, in a hydraulically driven bioreactor, can be a potential 3D tool and a key in this process (184).

Lastly, it was established two patient-centered screening tools for T2D, more precisely the "palette" model, based on molecular taxonomy, and the DIRECT-DETECT prediction model, composed by glycaemic deterioration biomarkers (159, 160, 185).

DISCUSSION

Based on the objectives of the IMI funded-projects and the results previously mentioned, we propose an integrated model addressing diabetes in its multiple dimensions, which includes two inter-dependent paths that should be executed in parallel, the first one being more scientific-oriented and the second one medical-oriented, as illustrated in **Figure 3**.

The scientific dimension would include the acquisition of more biological samples and genetic data and with the help of SUMMIT, IMIDIA, EBiSC, StemBANCC, EMIF, and IMI2PACT promote the research on β-cells as well as validate new biomarkers, genetic markers, patient stratification, discover more molecular mechanisms/pathways, and develop new treatments for T1D, T2D and diabetic complications. Besides, this approach aims at conducting clinical trials with more safety and efficacy endpoints through the application of those identified by SUMMIT, DIRECT, INNODIA, and BEAT-DKD to allow a marketing authorization of innovative medicines/therapeutics in a shorter time, less expensive and more focused on personalized medicine.

The medical dimension would include the use of predisposition markers developed by IMIDIA, DIRECT and INNODIA to identify people at higher risk of developing diabetes, with a particular interest in T2D, promoting the possibility of early intervention mainly in lifestyle habits, diet and physical exercise, and thus delaying the disease. Following the natural cycle of the disease, the objective would be to diagnose the recent-onset patients, through imaging technologies, tools and patient-centered models for clinicians developed by DIRECT, IMIDIA, INNODIA and RHAPSODY. Subsequently, the characterization of the subtype of patient and the treatment selection would be performed through the application of the DIRECT, INNODIA or RHAPSODY/BEAT-DKD stratification models and considering the inter-individual factors that impact the patient's response to the therapeutic agents identified by SUMMIT and DIRECT. The monitoring of disease progression would be possible in case of implementation of biomarkers, genetic markers and tools created by SUMMIT, IMIDIA, DIRECT, INNODIA, EMIF and RHAPSODY, with adaptations of pharmacological treatment dose or medicines changes in case of inadequate response. Additionally, with the use of biomarkers, genetic factors and tools developed by SUMMIT and BEAT-DKD, it would be possible to identify patients who during the progression of the disease, are more likely to develop diabetic complications, enabling to act in advance. With the application of imaging technologies developed

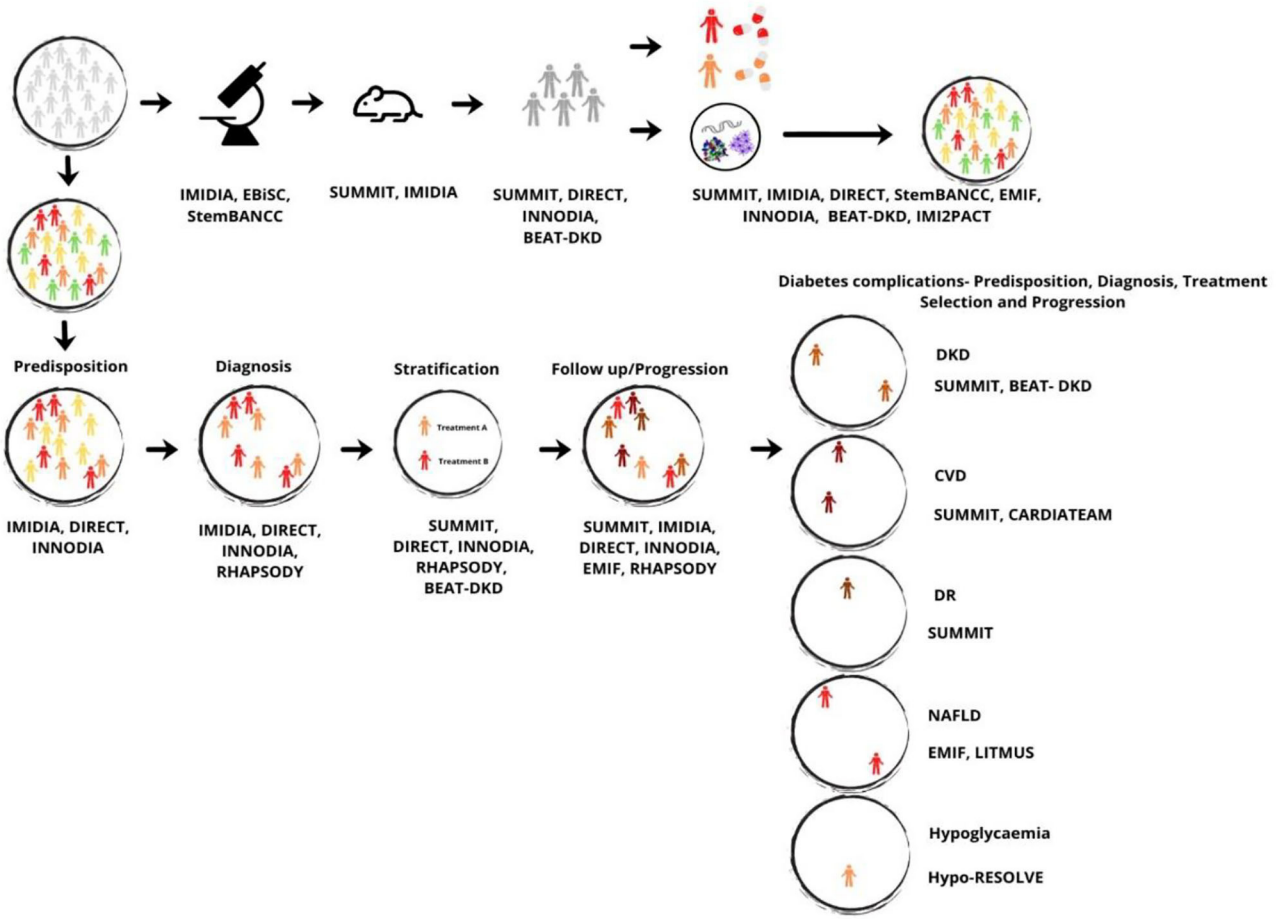


FIGURE 3 | Integrated vision model for diabetes, based on the objectives and results of the IMI funded-projects. Color meaning: gray, general population; green, individuals at low risk of diabetes; yellow, individuals at medium risk of diabetes; orange, individuals at medium-high risk of diabetes; red, individuals at high risk of diabetes; dark orange, individuals at high risk of DKD; dark red, individuals at high risk of CVD; brown, individuals at high risk of DR; light red, individuals at high risk of NAFLD; and light orange, individuals at high risk of hypoglycaemia. BEAT-DKD, Biomarker Enterprise to Attack DKD Project; CARDIATEAM, Cardiomyopathy in Type 2 Diabetes Mellitus Project; CVD, Cardiovascular diseases; DIRECT, Diabetes Research on Patient Stratification Project; DKD, Diabetic Kidney Disease; DR, Diabetic Retinopathy; EBiSC, European Bank for induced pluripotent Stem Cells Project; EMIF, European Medical Information Framework Project; Hypo-RESOLVE, Hypoglycaemia, Redefining Solutions for Better Lives Project; IMIDIA, Improving Beta-cell Function and Identification of Diagnostic Biomarkers for Treatment Monitoring in Diabetes Project; INNODIA, Translational Approaches to Disease Modifying Therapy of Type 1 Diabetes: An Innovative Approach Toward Understanding and Arresting Type 1 Diabetes Project; LITMUS, Liver Investigation: Testing Marker Utility in Steatohepatitis Project; NAFLD, Non-Alcoholic Fatty Liver disease; RHAPSODY, Assessing Risk and Progression of Prediabetes and Type 2 Diabetes to Enable Disease Modification Project; StemBANCC, Stem Cells for Biological Assays of Novel Medicines and Predictive Toxicology Project; SUMMIT, Surrogate Markers for Micro- and Macro-Vascular Hard Endpoints for Innovative Diabetes Tools Project.

by SUMMIT and EMIF and the information provided by BEAT-DKD, LITMUS, Hypo-RESOLVE, and CARDIATEAM, it would also be possible to predict the identification of patients with diabetic complications, especially diabetic nephropathy, diabetic retinopathy, cardiovascular disease, hypoglycemia, and non-Alcoholic Fatty Liver disease. Through the use of genetic factors and biomarkers developed by SUMMIT and BEAT-DKD, it would be desirable to select the best pharmacological treatment option according to the patient's characteristics and then monitor the follow-up to retard/stabilize its progression.

Summarizing, our integrated vision model supports a clinical model directed primarily and mainly at prevention, through the individual genetic and biological knowledge; as a first-line intervention, acting in the delay of diabetes onset; and in cases of diagnosis, to promote treatment according to the subtype of patients and monitor the progression of the disease. Only in this way, it will be possible to decrease the incidence and mortality rate of diabetes, provide an increase in the patient's quality of life, ensure sustainable people-centered health systems, and minimize direct and indirect diabetes-related costs in health systems.

Overall, it was found that the target & biomarker identification and innovative medicines axis have more published data. This was because these were major bottlenecks addressed by IMI 1 programme and included goals that corresponded to the key

unmet needs in Diabetes during the programme's execution period 2008–2013.

Our literature review is subject to some limitations. When collecting the projects' data, we found a large gap in their publication's library, mainly SUMMIT, IMIDIA, and DIRECT projects. On SUMMIT website, there were only publications between 2010 and 2014, however, on the Cordis database, we found publications up to 2018. Similarly, although the IMIDIA website only included publications from 2011 and 2012, the Cordis database had articles until 2014. Regarding the DIRECT project, its website had only assembled the publications of the participating companies, all published before obtaining funding. Other limitations include the unsuccessful response from the project's coordinators and co-coordinators, and the CORDIS database was also not updated and complete.

CONCLUSION

In order to reduce the incidence, the mortality rate, and the economic burden on healthcare systems, as well as to improve disease management, until October of 2019, IMI1 and IMI2 programmes funded 13 projects encompassing several bottlenecks identified for R&D and clinical practice in Diabetes area.

Taking into account the scientific production available by these projects, we prepared a joint vision model including two paths: one scientific-oriented and the other medical-oriented. The scientific dimension integrates the current knowledge regarding this disease, research tools, as well as clinical trial designs and endpoints to allow marketing authorization of new effective and safer medicines in a shorter time and less expensive. The medical dimension includes the application of predisposition markers (biological and genetic), diagnostic tools, stratification models, treatment selection, and monitoring the progression of the disease to prevent/delay the development of diabetic complications.

As IMI programmes fostered the enhancing of knowledge and the improvement of the medical practice (with better tools, medicines, and prediction models), being a big step for the implementation of personalized medicine, it is clear that this initiative has an important role in the scientific advances that have occurred in recent years.

In terms of future perspectives, the biggest bottleneck will be the implementation of the proposed joint vision model, or a similar one, into the clinical practice, although all IMI-funded projects highlight this trend as the only one able to provide an effective response in the treatment of chronic diseases, in particular diabetes, and there are already proves of shifts in the paradigm. Nevertheless, the involvement of key stakeholders, including patients, will always be essential to the success of this process.

AUTHOR CONTRIBUTIONS

MB was responsible for the conduct of the study, data extraction and analysis and drafted the manuscript. BS-L had the original idea for the manuscript and supervised study conduct. BS-L and CT participated in the collection of additional literature, contributed to the writing of the manuscript and revised it critically for important intellectual content. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.688438/full#supplementary-material

REFERENCES

1. Innovative Medicines Initiative. *The Innovative Medicines Initiative (IMI) Research Agenda - Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society*. (2008). Available online at: http://www.imi.europa.eu/sites/default/files/uploads/documents/SRArevised2011.pdf%5Cnhttp://www.imi.europa.eu/sites/default/files/uploads/documents/imi-gb-006v2-15022008-research-agenda_en.pdf (accessed January 22, 2019).
2. Centre for Innovation in Regulatory Science (CIRS). *Socio-Economic Impact Report on IMI1 projects*. London: Clarivate's Centre (2021).
3. *COUNCIL REGULATION (EC) No 73/2008 of 20 December 2007*. Official Journal of the European Union (2008).
4. Innovative Medicines Initiative. *History – the IMI Story so Far*. (2014). Available online at: https://www.imi.europa.eu/about-imi/history-imi-story-so-far (accessed January 21, 2019).
5. IMI Publications. *The Right Prevention and Treatment for the Right Patient at the Right Time - Strategic Reseach Data for Innovative Medicines Initiative 2*. Brussels: IMI Publications (2014).
6. Council Regulation (EU) No 557/2014 of 6 May 2014. *Off J Eur Union* (2014).
7. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL. *Harrison's Principles of Intermal Medicine*. 19th ed. New York, NY: McGraw-Hill Education (2015).
8. World Health Organization. *Global Report on Diabetes*. Geneva: World Health Organization (2016).
9. Baynest HW. Classification, pathophysiology, diagnosis and management of diabetes mellitus. *J Diabetes Metab.* (2015) 6:1–9. doi: 10.4172/2155-6156.1000541
10. World Health Organization. *Diabetes*. Geneva: World Health Organization (2018).
11. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol.* (2018) 14:88–98. doi: 10.1038/nrendo.2017.151
12. World Health Organization. *The top 10 Causes of Death*. Geneva: World Health Organization. (2018).
13. *Project Factsheets | Diabetes & metabolic disorders | IMI Innovative Medicines Initiative*. Available online at: https://www.imi.europa.eu/projects-results/project-factsheets?keywords=&status=All&call=All&programmes=All&disease_areas=DA4&products=All&tools=All (accessed August 19, 2019).
14. Meyerovich K, Violato NM, Fukaya M, Dirix V, Pachera N, Marselli L, et al. MCL-1 is a key anti-apoptotic protein in human and rodent pancreatic β-cells. *Diabetes.* (2018) 66:1–46. doi: 10.2337/db16-1252
15. Demine S, Balhuizen A, Debaille V, Joosten L, Fereau M, Chilla SNM, et al. Imaging of human insulin secreting cells with GD-dotA-P88, a paramagnetic contrast agent targeting the beta cell biomarker FxyD2γA. *Molecules.* (2018) 23:1–16. doi: 10.3390/molecules23092100

16. Paula FMM, Leite NC, Borck PC, Freitas-Dias R, Cnop M, Chacon-Mikahil MPT, et al. Exercise training protects human and rodent β cells against endoplasmic reticulum stress and apoptosis. *FASEB J.* (2018) 32:1524–36. doi: 10.1096/fj.201700710R
17. Mathieu C, Lahesmaa R, Bonifacio E, Achenbach P, Tree T. Immunological biomarkers for the development and progression of type 1 diabetes. *Diabetologia.* (2018) 61:2252–8. doi: 10.1007/s00125-018-4726-8
18. Colli ML, Hill JLE, Marroquí L, Chaffey J, Dos Santos RS, Leete P, et al. PDL1 is expressed in the islets of people with type 1 diabetes and is up-regulated by interferons-α and-γ via IRF1 induction. *EBioMedicine.* (2018) 36:367–75. doi: 10.1016/j.ebiom.2018.09.040
19. Buitinga M, Callebaut A, Sodré FMC, Crèvecoeur I, Blahnik-Fagan G, Yang ML, et al. Inflammation-induced citrullinated glucose-regulated protein 78 elicits immune responses in human type 1 diabetes. *Diabetes.* (2018) 67:2337–48. doi: 10.2337/db18-0295
20. Müller D, Telieps T, Eugster A, Weinzierl C, Jolink M, Ziegler AG, et al. Novel minor HLA DR associated antigens in type 1 diabetes. *Clin Immunol.* (2018) 194:87–91. doi: 10.1016/j.clim.2018.07.001
21. Gonzalez-Duque S, Azoury ME, Colli ML, Afonso G, Turatsinze JV, Nigi L, et al. Conventional and neo-antigenic peptides presented by β cells are targeted by circulating naïve CD8+ T Cells in type 1 diabetic and healthy donors. *Cell Metab.* (2018) 28:946–60. doi: 10.1016/j.cmet.2018.07.007
22. Harbige J, Eichmann M, Peakman M. New insights into non-conventional epitopes as T cell targets: the missing link for breaking immune tolerance in autoimmune disease? *J Autoimmun.* (2017) 84:12–20. doi: 10.1016/j.jaut.2017.08.001
23. Dotta F, Ventriglia G, Snowhite IV, Pugliese A. MicroRNAs: markers of β-cell stress and autoimmunity. *Curr Opin Endocrinol Diabetes Obes.* (2018) 25:237–45. doi: 10.1097/MED.0000000000000420
24. Santos RS, Marroqui L, Grieco FA, Marselli L, Suleiman M, Henz SR, et al. Protective role of complement C3 against cytokine-mediated β-cell apoptosis. *Endocrinology.* (2017) 158:2503–21. doi: 10.1210/en.2017-00104
25. Haid M, Muschet C, Wahl S, Römisch-Margl W, Prehn C, Möller G, et al. Long-term stability of human plasma metabolites during storage at−80°c. *J Proteome Res.* (2018) 17:203–11. doi: 10.1021/acs.jproteome.7b00518
26. Richards P, Rachdi L, Oshima M, Marchetti P, Bugliani M, Armanet M, et al. MondoA is an essential glucose responsive transcription factor in human pancreatic beta cells. *Diabetes.* (2018) 67:461–72. doi: 10.2337/db17-0595
27. Diedisheim M, Oshima M, Albagli O, Huldt CW, Ahlstedt I, Clausen M, et al. Modeling human pancreatic beta cell dedifferentiation. *Mol Metab.* (2018) 10:74–86. doi: 10.1016/j.molmet.2018.02.002
28. Gerst F, Jaghutriz BA, Staiger H, Schulte AM, Lorza-Gil E, Kaiser G, et al. The expression of aldolase B in islets is negatively associated with insulin secretion in humans. *J Clin Endocrinol Metab.* (2018) 103:4373–83. doi: 10.1210/jc.2018-00791
29. Lamerz J, Friedlein A, Soder N, Cutler P, Döbeli H. Determination of free desmosine in human plasma and its application in two experimental medicine studies. *Anal Biochem.* (2013) 436:127–36. doi: 10.1016/j.ab.2013.01.012
30. SUMMIT. *IMI1 Final Project Report Public Summary - SUrrogate Markers for Vascular Micro- and Macrovascular Hard Endpoints for Innovative Diabetes Tools*. SUMMIT (2016).
31. Lindenmeyer MT, Kretzler M. Renal biopsy-driven molecular target identification in glomerular disease. *Pflugers Arch Eur J Physiol.* (2017) 469:1021–8. doi: 10.1007/s00424-017-2006-y
32. Koppelstaetter C, Leierer J, Rudnicki M, Kerschbaum J, Kronbichler A, Melk A, et al. Computational drug screening identifies compounds targeting renal age-associated molecular profiles. *Comput Struct Biotechnol J.* (2019) 17:843–53. doi: 10.1016/j.csbj.2019.06.019
33. Wolf M, de Boer A, Sharma K, Boor P, Leiner T, Sunder-Plassmann G, et al. Magnetic resonance imaging T1- and T2-mapping to assess renal structure and function: a systematic review and statement paper. *Nephrol Dial Transplant.* (2018) 33:ii41–50. doi: 10.1093/ndt/gfy198
34. Barreiro K, Holthofer H. Urinary extracellular vesicles. A promising shortcut to novel biomarker discoveries. *Cell Tissue Res.* (2017) 369:217–27. doi: 10.1007/s00441-017-2621-0
35. Hamidi H, Kretzler M. Systems biology approaches to identify disease mechanisms and facilitate targeted therapy in the management of glomerular disease. *Physiol Behav.* (2017) 176:139–48. doi: 10.1097/MNH.0000000000000446
36. Henique C, Bollée G, Loyer X, Grahammer F, Dhaun N, Camus M, et al. Genetic and pharmacological inhibition of microRNA-92a maintains podocyte cell cycle quiescence and limits crescentic glomerulonephritis. *Nat Commun.* (2017) 8:1829. doi: 10.1038/s41467-017-01885-7
37. Idzerda NMA, Persson F, Pena MJ, Brenner BM, Brunel P, Chaturvedi N, et al. N-terminal pro-brain natriuretic peptide (NT-proBNP) predicts the cardio-renal response to aliskiren in patients with type 2 diabetes at high renal and cardiovascular risk. *Diabetes Obes Metab.* (2018) 20:2899–904. doi: 10.1111/dom.13465
38. Perco P, Mayer G. Endogenous factors and mechanisms of renoprotection and renal repair. *Eur J Clin Invest.* (2018) 48:1–13. doi: 10.1111/eci.12914
39. Perco P, Ju W, Kerschbaum J, Leierer J, Menon R, Zhu C, et al. Identification of dicarbonyl and L-xylulose reductase as a therapeutic target in human chronic kidney disease. *JCI Insight.* (2019) 4:e128120. doi: 10.1172/jci.insight.128120
40. Silveira A, McLeod O, Strawbridge RJ, Gertow K, Sennblad B, Baldassarre D, et al. Plasma IL-5 concentration and subclinical carotid atherosclerosis. *Atherosclerosis.* (2015) 239:125–30. doi: 10.1016/j.atherosclerosis.2014.12.046
41. Deleskog A, Piksasova O, Silveira A, Gertow K, Baldassarre D, Veglia F, et al. Serum 25-hydroxyvitamin D concentration in subclinical carotid atherosclerosis. *Arterioscler Thromb Vasc Biol.* (2013) 33:2633–8. doi: 10.1161/ATVBAHA.113.301593
42. Kinnunen K, Heinonen SE, Kalesnykas G, Laidinen S, Uusitalo-Järvinen H, Uusitalo H, et al. LDLR-/-ApoB100/100 mice with insulin-like growth factor II overexpression reveal a novel form of retinopathy with photoreceptor atrophy and altered morphology of the retina. *Mol Vis.* (2013) 19:1723–33.
43. Sandholm N, McKnight AJ, Salem RM, Brennan EP, Forsblom C, Harjutsalo V, et al. Chromosome 2q31.1 associates with ESRD in women with type 1 diabetes. *J Am Soc Nephrol.* (2013) 24:1537–43. doi: 10.1681/ASN.2012111122
44. Bötticher G, Sturm D, Ehehalt F, Knoch KP, Kersting S, Grützmann R, et al. Isolation of human islets from partially pancreatectomized patients. *J Vis Exp*. (2011) 53:2962. doi: 10.3791/2962
45. Ravassard P, Hazhouz Y, Pechberty S, Bricout-neveu E, Armanet M, Czernichow P, et al. A genetically engineered human pancreatic β cell line exhibiting glucose-inducible insulin secretion. *J Clin Invest.* (2011). 121:3589–97. doi: 10.1172/JCI58447
46. Rutter GA, Herrera PL, Cruciani-Guglielmacci C, Mourougavelou V, Magnan C, da Silva Xavier G, et al. Pancreatic alpha cell-selective deletion of Tcf7l2 impairs glucagon secretion and counter-regulatory responses to hypoglycaemia in mice. *Diabetologia.* (2017) 60:1043–50. doi: 10.1007/s00125-017-4242-2
47. Lamprianou S, Immonen R, Nabuurs C, Gjinovci A, Vinet L, Montet XCR, et al. High-resolution magnetic resonance imaging quantitatively detects individual pancreatic islets. *Diabetes.* (2011) 60:2853–60. doi: 10.2337/db11-0726
48. Kaminski MT, Lenzen S, Baltrusch S. Real-time analysis of intracellular glucose and calcium in pancreatic beta cells by fluorescence microscopy. *Biochim Biophys Acta Mol Cell Res.* (2012) 1823:1697–707. doi: 10.1016/j.bbamcr.2012.06.022
49. Rutter GA, Weitz J, Kleeberg M, Siddiq A, Meinel J, Burdet F, et al. Systems biology of the IMIDIA biobank from organ donors and pancreatectomised patients defines a novel transcriptomic signature of islets from individuals with type 2 diabetes. *Diabetologia.* (2017) 61:641–57. doi: 10.1007/s00125-017-4500-3
50. Donnelly LA, Zhou K, Doney ASF, Jennison C, Franks PW, Pearson ER. Rates of glycaemic deterioration in a real-world population with type 2 diabetes. *Diabetologia.* (2018) 61:607–15. doi: 10.1007/s00125-017-4519-5
51. Babbar R, Heni M, Peter A, de Angelis MH, Häring HU, Fritsche A, et al. Prediction of glucose tolerance without an oral glucose tolerance test. *Front Endocrinol (Lausanne).* (2018) 9:82. doi: 10.3389/fendo.2018.00082
52. Willemsen RH, Burling K, Barker P, Ackland F, Dias RP, Edge J, et al. Frequent monitoring of C-peptide levels in newly diagnosed type 1 subjects using dried blood spots collected at home. *J Clin Endocrinol Metab.* (2018) 103:3350–8. doi: 10.1210/jc.2018-00500

53. Pociot F. Capturing residual beta cell function in type 1 diabetes. *Diabetologia.* (2019) 62:28–32. doi: 10.1007/s00125-018-4768-y
54. Hyysalo J, Männistö VT, Zhou Y, Arola J, Kärjä V, Leivonen M, et al. A population-based study on the prevalence of NASH using scores validated against liver histology. *J Hepatol.* (2014) 60:839–46. doi: 10.1016/j.jhep.2013.12.009
55. Orešič M, Hyötyläinen T, Kotronen A, Gopalacharyulu P, Nygren H, Arola J, et al. Prediction of non-alcoholic fatty-liver disease and liver fat content by serum molecular lipids. *Diabetologia.* (2013) 56:2266–74. doi: 10.1007/s00125-013-2981-2
56. Albertini M, Postma J, Jani K. *SUMMIT & so Forth. (05)*. SUMMIT (2013).
57. Hellberg S, Silvola JMU, Kiugel M, Liljenbäck H, Metsälä O, Viljanen T, et al. Type 2 diabetes enhances arterial uptake of choline in atherosclerotic mice: an imaging study with positron emission tomography tracer 18F-fluoromethylcholine. *Cardiovasc Diabetol.* (2016) 15:1–13. doi: 10.1186/s12933-016-0340-6
58. Malovini A, Barbarini N, Bellazzi R, De Michelis F. Hierarchical Naive Bayes for genetic association studies. *BMC Bioinformatics.* (2012) 13(Suppl. 1):S6. doi: 10.1186/1471-2105-13-S14-S6
59. Sambo F, Trifoglio E, Di Camillo B, Toffolo GM, Cobelli C. Bag of Naïve Bayes: biomarker selection and classification from genome-wide SNP data. *BMC Bioinformatics.* (2012) 13(Suppl. 1):S2. doi: 10.1186/1471-2105-13-S14-S2
60. Sambo F, Malovini A, Sandholm N, Stavarachi M, Forsblom C, Mäkinen VP, et al. Novel genetic susceptibility loci for diabetic end-stage renal disease identified through robust naive Bayes classification. *Diabetologia.* (2014) 57:1611–22. doi: 10.1007/s00125-014-3256-2
61. Di Camillo B, Sambo F, Toffolo G, Cobelli C. ABACUS: an entropy-based cumulative bivariate statistic robust to rare variants and different direction of genotype effect. *Bioinformatics.* (2014) 30:384–91. doi: 10.1093/bioinformatics/btt697
62. Sandor C, Beer NL, Webber C. Diverse type 2 diabetes genetic risk factors functionally converge in a phenotype-focused gene network. *PLoS Comput Biol.* (2017) 13:1–23. doi: 10.1371/journal.pcbi.1005816
63. Beer NL, Gloyn AL. Genome-edited human stem cell-derived beta cells: a powerful tool for drilling down on type 2 diabetes GWAS biology. *F1000Research.* (2016) 5:1711. doi: 10.12688/f1000research.8682.1
64. Xie W, Wood AR, Lyssenko V, Weedon MN, Knowles JW, Alkayyali S, et al. Genetic variants associated with glycine metabolism and their role in insulin sensitivity and type 2 diabetes. *Diabetes.* (2013) 62:2141–50. doi: 10.2337/db12-0876
65. Ahluwalia TS, Lindholm E, Groop LC. Common variants in CNDP1 and CNDP2, and risk of nephropathy in type 2 diabetes. *Diabetologia.* (2011) 54:2295–302. doi: 10.1007/s00125-011-2178-5
66. Sandholm N, Salem RM, McKnight AJ, Brennan EP, Forsblom C, Isakova T, et al. New susceptibility loci associated with kidney disease in type 1 diabetes. *PLoS Genet.* (2012) 8:e1002921. doi: 10.1371/journal.pgen.1002921
67. Fagerholm E, Ahlqvist E, Forsblom C, Sandholm N, Syreeni A, Parkkonen M, et al. SNP in the genome-wide association study hotspot on chromosome 9p21 confers susceptibility to diabetic nephropathy in type 1 diabetes. *Diabetologia.* (2012) 55:2386–93. doi: 10.1007/s00125-012-2587-0
68. He B, Österholm AM, Ojala JRM, Andersson AC, Tryggvason K. A remote cis-acting variant at 3q links glomerular NCK1 to diabetic nephropathy. *PLoS ONE.* (2013) 8:e56414. doi: 10.1371/journal.pone.0056414
69. Sandholm N, Forsblom C, Mäkinen VP, McKnight AJ, Österholm AM, He B, et al. Genome-wide association study of urinary albumin excretion rate in patients with type 1 diabetes. *Diabetologia.* (2014) 57:1143–53. doi: 10.1007/s00125-014-3202-3
70. Strawbridge RJ, Hilding A, Silveira A, Österholm C, Sennblad B, McLeod O, et al. Soluble CD93 is involved in metabolic dysregulation but does not influence carotid intima-media thickness. *Diabetes.* (2016) 65:2888–99. doi: 10.2337/db15-1333
71. Zeng B, Chen GL, Garcia-Vaz E, Bhandari S, Daskoulidou N, Berglund LM, et al. Orai channels are critical for receptor-mediated endocytosis of albumin. *Nat Commun.* (2017) 8:1920. doi: 10.1038/s41467-017-02094-y
72. Williams WW, Salem RM, McKnight AJ, Sandholm N, Forsblom C, Taylor A, et al. Association testing of previously reported variants in a large case-control meta-analysis of diabetic nephropathy. *Diabetes.* (2012) 61:2187–94. doi: 10.2337/db11-0751
73. Rutter J, Semplici F, Meur G, Fontés G, Diraison F, Fogarty S, et al. Human mutation within Per-Arnt-Sim (PAS) domain-containing Protein Kinase (PASK) causes basal insulin hypersecretion. *J Biol Chem.* (2011) 286:44005–14. doi: 10.1074/jbc.M111.254995
74. Di Paola R, Caporarello N, Marucci A, Dimatteo C, Iadicicco C, Del Guerra S, et al. ENPP1 affects insulin action and secretion: evidences from in vitro studies. *PLoS ONE.* (2011) 6:e19462. doi: 10.1371/journal.pone.0019462
75. Locke JM, Xavier GDS, Rutter GA, Harries LW. An alternative polyadenylation signal in TCF7L2 generates isoforms that inhibit T cell factor / lymphoid-enhancer factor (TCF/LEF) -dependent target genes. *Diabetologia*. (2011). 2:3078–82. doi: 10.1007/s00125-011-2290-6
76. Bugliani M, Liechti R, Cheon H, Suleiman M, Marselli L, Kirkpatrick C, et al. Microarray analysis of isolated human islet transcriptome in type 2 diabetes and the role of the ubiquitin-proteasome system in pancreatic beta cell dysfunction. *Mol Cell Endocrinol.* (2013) 367:1–10. doi: 10.1016/j.mce.2012.12.001
77. Pasquali L, Gaulton KJ, Rodríguez-seguí SA, Gómez-marín C, Bunt M Van De, Ponsa-cobas J, et al. Pancreatic islet enhancer clusters enriched in type 2 diabetes risk – associated variants. *Nat Genet*. (2014). 46:136–43. doi: 10.1038/ng.2870
78. Poveda A, Koivula RW, Ahmad S, Barroso I, Hallmans G, Johansson I, et al. Innate biology versus lifestyle behaviour in the aetiology of obesity and type 2 diabetes: the GLACIER Study. *Diabetologia.* (2016) 59:462–71. doi: 10.1007/s00125-015-3818-y
79. Ahmad S, Rukh G, Varga TV, Ali A, Kurbasic A, Shungin D, et al. Gene × physical activity interactions in obesity: combined analysis of 111,421 individuals of European Ancestry. *PLoS Genet.* (2013) 9:1–9. doi: 10.1371/journal.pgen.1003607
80. Wood AR, Jonsson A, Jackson AU, Wang N, Van Leewen N, Palmer ND, et al. A genome-wide association study of IVGTT-based measures of first-phase insulin secretion refines the underlying physiology of type 2 diabetes variants. *Diabetes.* (2017) 66:2296–309. doi: 10.2337/db16-1452
81. Franks PW, McCarthy MI. Exposing the exposures responsible for type 2 diabetes and obesity. *Science.* (2016) 354:69–73. doi: 10.1126/science.aaf5094
82. Gudmundsdottir V, Pedersen HK, Allebrandt KV, Brorsson C, van Leeuwen N, Banasik K, et al. Integrative network analysis highlights biological processes underlying GLP-1 stimulated insulin secretion: a DIRECT study. *PLoS ONE.* (2018) 13:1–19. doi: 10.1371/journal.pone.0189886
83. Payne F, Lim K, Girousse A, Brown RJ, Kory N, Robbins A, et al. Mutations disrupting the Kennedy phosphatidylcholine pathway in humans with congenital lipodystrophy and fatty liver disease. *Proc Natl Acad Sci.* (2014) 111:8901–6. doi: 10.1073/pnas.1408523111
84. Payne F, Colnaghi R, Rocha N, Seth A, Harris J, Carpenter G, et al. Hypomorphism in human NSMCE2 linked to primordial dwarfism and insulin resistance. *J Clin Invest.* (2014) 124:4028–38. doi: 10.1172/JCI73264
85. Cederberg H, Stančáková A, Kuusisto J, Laakso M, Smith U. Family history of type 2 diabetes increases the risk of both obesity and its complications: is type 2 diabetes a disease of inappropriate lipid storage? *J Intern Med.* (2015) 277:540–51. doi: 10.1111/joim.12289
86. Lotta LA, Scott RA, Sharp SJ, Burgess S, Luan J, Tillin T, et al. Genetic predisposition to an impaired metabolism of the branched-chain amino acids and risk of type 2 diabetes: a mendelian randomisation analysis. *PLoS Med.* (2016) 13:1–22. doi: 10.1371/journal.pmed.1002179
87. Hogling DE, Petrus P, Gao H, Bäckdahl J, Dahlman I, Laurencikiene J, et al. Adipose and circulating CCL18 levels associate with metabolic risk factors in women. *J Clin Endocrinol Metab*. (2016) 101:4021–9. doi: 10.1210/jc.2016-2390
88. Huang-Doran I, Tomlinson P, Payne F, Gast A, Sleigh A, Bottomley W, et al. Insulin resistance uncoupled from dyslipidemia due to C-terminal PIK3R1 mutations. *JCI Insight.* (2016) 1:1–15. doi: 10.1172/jci.insight.88766
89. Yew Tan C, Virtue S, Murfitt S, Robert LD, Phua YH, Dale M, et al. Adipose tissue fatty acid chain length and mono-unsaturation increases with obesity and insulin resistance. *Sci Rep.* (2015) 5:1–10. doi: 10.1038/srep18366

90. Balboa D, Saarimäki-Vire J, Borshagovski D, Survila M, Lindholm P, Galli E, et al. Insulin mutations impair beta-cell development in a patient-derived iPSC model of neonatal diabetes. *Elife.* (2018) 7:1–35. doi: 10.7554/eLife.38519
91. Grieco FA, Sebastiani G, Juan-Mateu J, Villate O, Marroqui L, Ladrière L, et al. MicroRNAs miR-23a-3p, miR-23b-3p, and miR-149-5p regulate the expression of proapoptotic bh3-only proteins DP5 and PUMA in human pancreatic β-cells. *Diabetes.* (2017) 66:100–12. doi: 10.2337/db16-0592
92. Reinauer C, Rosenbauer J, Bächle C, Herder C, Roden M, Ellard S, et al. The clinical course of patients with preschool manifestation of type 1 diabetes is independent of the HLA DR-DQ genotype. *Genes (Basel).* (2017) 8:2–17. doi: 10.3390/genes8050146
93. Dos Santos RS, Marroqui L, Velayos T, Olazagoitia-Garmendia A, Jauregi-Miguel A, Castellanos-Rubio A, et al. DEXI, a candidate gene for type 1 diabetes, modulates rat and human pancreatic beta cell inflammation via regulation of the type I IFN/STAT signalling pathway. *Diabetologia.* (2019) 62:459–72. doi: 10.1007/s00125-018-4782-0
94. Cosentino C, Toivonen S, Villamil ED, Atta M, Ravanat JL, Demine S, et al. Pancreatic -cell tRNA hypomethylation and fragmentation link TRMT10A deficiency with diabetes. *Nucleic Acids Res.* (2018) 46:10302–18. doi: 10.1093/nar/gky839
95. Slieker RC, van der Heijden AAWA, van Leeuwen N, Mei H, Nijpels G, Beulens JW, et al. HbA1c is associated with altered expression in blood of cell cycle- and immune response-related genes. *Diabetologia.* (2018) 61:138–46. doi: 10.1007/s00125-017-4467-0
96. Zhou K, Donnelly L, Yang J, Li M, Deshmukh H, Zuydam N Van, et al. Heritability of variation in glycaemic response to metformin: a genome-wide complex trait analysis. *Lancet Diabetes Endocrinol.* (2014) 2:481–7. doi: 10.1016/S2213-8587(14)70050-6
97. Rocca B, Dragani A, Pagliaccia F. Identifying determinants of variability to tailor aspirin therapy. *Expert Rev Cardiovasc Ther.* (2013) 11:365–79. doi: 10.1586/erc.12.144
98. Rocca B, Santilli F, Pitocco D, Mucci L, Petrucci G, Vitacolonna E, et al. The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes. *J Thromb Haemost.* (2012) 10:1220–30. doi: 10.1111/j.1538-7836.2012.04723.x
99. Franks PW, Pearson E, Florez JC. Gene-environment and gene-treatment interactions in type 2 diabetes: Progress, pitfalls, and prospects. *Diabetes Care.* (2013) 36:1413–21. doi: 10.2337/dc12-2211
100. Pearson ER. Personalized medicine in diabetes: the role of "omics" and biomarkers. *Diabet Med.* (2016) 33:712–7. doi: 10.1111/dme.13075
101. Rouskas K, Cauchi S, Raverdy V, Yengo L, Froguel P, Pattou F. Weight loss independent association of TCF7 L2 gene polymorphism with fasting blood glucose after Roux-en-Y gastric bypass in type 2 diabetic patients. *Surg Obes Relat Dis.* (2014) 10:679–83. doi: 10.1016/j.soard.2013.12.016
102. Apperloo EM, Pena MJ, Zeeuw D, Denig P, Heerspink HJL. Individual variability in response to renin angiotensin aldosterone system inhibition predicts cardiovascular outcome in patients with type 2 diabetes: a primary care cohort study. *Diabetes Obes Metab.* (2018) 20:1377–83. doi: 10.1111/dom.13226
103. Idzerda NMA, Pena MJ, Heerspink HJL. Personalized medicine in diabetic kidney disease: a novel approach to improve trial design and patient outcomes. *Curr Opin Nephrol Hypertens.* (2018) 27:426–32. doi: 10.1097/MNH.0000000000000447
104. Franks PW, Atabaki-Pasdar N. Causal inference in obesity research. *J Intern Med.* (2017) 281:222–32. doi: 10.1111/joim.12577
105. Lotta LA, Abbasi A, Sharp SJ, Sahlqvist AS, Waterworth D, Brosnan JM, et al. Definitions of metabolic health and risk of future type 2 diabetes in body mass index categories : a systematic review and network. *Diabetes Care.* (2016). 38:2177–87. doi: 10.2337/dc15-1218
106. Sattar N, Gill JMR. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. *Lancet Diabetes Endocrinol.* (2015) 3:1004–16. doi: 10.1016/S2213-8587(15)00326-5
107. Schwandt A, Hermann JM, Rosenbauer J, Boettcher C, Dunstheimer D, Grulich-Henn J, et al. Longitudinal trajectories of metaboliccontrol from childhood to young adulthood in type 1 diabetes from a large German/ austrian registry: a group-based modeling approach. *Diabetes Care.* (2017) 40:309–16. doi: 10.2337/dc16-1625
108. Ahlqvist E, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol.* (2018) 6:361–9. doi: 10.1016/S2213-8587(18)30051-2
109. Magnan C, Thorens B, Campana M, Lenoir V, Prip-Buus C, Hainault I, et al. Protective role of the ELOVL2/docosahexaenoic acid axis in glucolipotoxicity-induced apoptosis in rodent beta cells and human islets. *Diabetologia.* (2018) 61:1780–93. doi: 10.1007/s00125-018-4629-8
110. Lortz S, Gurgul-Convey E, Naujok O, Lenzen S. Overexpression of the antioxidant enzyme catalase does not interfere with the glucose responsiveness of insulin-secreting INS-1E cells and rat islets. *Diabetologia.* (2013) 56:774–82. doi: 10.1007/s00125-012-2823-7
111. Klee P, Allagnat F, Pontes H, Cederroth M, Charollais A, Caille D, et al. Connexins protect mouse pancreatic β cells against apoptosis. *J Clin Investig.* (2011) 121:4870–9. doi: 10.1172/JCI40509
112. Mehmeti I, Gurgul-convey E, Lenzen S, Lortz S. Induction of the intrinsic apoptosis pathway in insulin-secreting cells is dependent on oxidative damage of mitochondria but independent of caspase-12 activation. *BBA - Mol Cell Res.* (2011) 1813:1827–35. doi: 10.1016/j.bbamcr.2011.06.022
113. Gurgul-convey E, Mehmeti I, Lortz S. Cytokine toxicity in insulin-producing cells is mediated by nitro-oxidative stress-induced hydroxyl radical formation in mitochondria. *J Mol Med (Berl).* (2011) 89:785–98. doi: 10.1007/s00109-011-0747-1
114. Efrat S. Mechanisms of adult human β-cell in vitro dedifferentiation and redifferentiation. *Diabetes Obes Metab.* (2016) 18:97–101. doi: 10.1111/dom.12724
115. Soggia A, Ramond C, Akiyama H, Scharfmann R, Duvillie B. von Hippel–Lindau gene disruption in mouse pancreatic progenitors and its consequences on endocrine differentiation *in vivo*: importance of HIF1-α and VEGF-A upregulation. *Diabetologia.* (2014) 57:2348–56. doi: 10.1007/s00125-014-3365-y
116. Honoré C, Rescan C, Hald J, McGrath PS, Petersen MBK, Hansson M, et al. Revisiting the immunocytochemical detection of Neurogenin 3 expression in mouse and man. *Diabetes Obes Metab.* (2016) 18:10–22. doi: 10.1111/dom.12718
117. Ramond C, Glaser N, Berthault C, Ameri J, Kirkegaard JS, Hansson M, et al. Reconstructing human pancreatic differentiation by mapping specific cell populations during development. *Elife.* (2017) 6:1–22. doi: 10.7554/eLife.27564
118. Hoarau E, Chandra V, Rustin P, Scharfmann R, Duvillie B. Pro-oxidant/antioxidant balance controls pancreatic β-cell differentiation through the ERK1/2 pathway. *Cell Death Dis.* (2014) 5:e1487–10. doi: 10.1038/cddis.2014.441
119. Rachdi L, Kariyawasam D, Guez F, Aïello V, Arbonés ML, Janel N, et al. Dyrk1a haploinsufficiency induces diabetes in mice through decreased pancreatic beta cell mass. *Diabetologia.* (2014) 57:960–9. doi: 10.1007/s00125-014-3174-3
120. Vig S, Buitinga M, Rondas D, Crèvecoeur I, van Zandvoort M, Waelkens E, et al. Cytokine-induced translocation of GRP78 to the plasma membrane triggers a pro-apoptotic feedback loop in pancreatic beta cells. *Cell Death Dis.* (2019) 10:309. doi: 10.1038/s41419-019-1518-0
121. Marroqui L, Santos RS, Op de beeck A, Coomans de Brachène A, Marselli L, Marchetti P, et al. Interferon-α mediates human beta cell HLA class I overexpression, endoplasmic reticulum stress and apoptosis, three hallmarks of early human type 1 diabetes. *Diabetologia.* (2017) 60:656–67. doi: 10.1007/s00125-016-4201-3
122. Bugliani M, Syed F, Paula FMM, Omar BA, Suleiman M, Mossuto S, et al. DPP-4 is expressed in human pancreatic beta cells and its direct inhibition improves beta cell function and survival in type 2 diabetes. *Mol Cell Endocrinol.* (2018) 473:186–93. doi: 10.1016/j.mce.2018.01.019
123. Yeo L, Lorenc A, Eichmann M, Pujol-Autonell I, Skowera A, Peakman M, et al. Autoreactive T effector memory differentiation mirrors β cell function in type 1 diabetes. *J Clin Invest.* (2018) 128:3460–74. doi: 10.1172/JCI120555
124. Tesovnik T, Kovac J, Hovnik T, Dovc K, Bratina N, Battelino T, et al. Association of glycemic control and cell stress with

telomere attrition in type 1 diabetes. *JAMA Pediatr.* (2018) 172:879–81. doi: 10.1001/jamapediatrics.2018.1175
125. Prinz N, Schwandt A, Becker M, Denzer C, Flury M, Fritsch M, et al. Trajectories of body mass index from childhood to young adulthood among patients with type 1 diabetes—a longitudinal group-based modeling approach based on the DPV registry. *J Pediatr.* (2018) 201:78–85.e4. doi: 10.1016/j.jpeds.2018.05.014
126. Zhou Y, Llauradó G, Orešič M, Hyötyläinen T, Orho-Melander M, Yki-Järvinen H. Circulating triacylglycerol signatures and insulin sensitivity in NAFLD associated with the E167K variant in TM6SF2. *J Hepatol.* (2015) 62:657–63. doi: 10.1016/j.jhep.2014.10.010
127. Eriksson-Hogling D, Andersson DP, Bäckdahl J, Hoffstedt J, Rössner S, Thorell A, et al. Adipose tissue morphology predicts improved insulin sensitivity following moderate or pronounced weight loss. *Int J Obes.* (2015) 39:893–8. doi: 10.1038/ijo.2015.18
128. Dahlman I, Sinha I, Gao H, Brodin D, Thorell A, Rydén M, et al. The fat cell epigenetic signature in post-obese women is characterized by global hypomethylation and differential DNA methylation of adipogenesis genes. *Int J Obes.* (2015) 39:910–9. doi: 10.1038/ijo.2015.31
129. Sattar N, Gill JMR. Type 2 diabetes as a disease of ectopic fat? *BMC Med.* (2014) 12:1–6. doi: 10.1186/s12916-014-0123-4
130. Eliasson B, Rawshani A, Axelsen M, Hammarstedt A, Smith U. Cephalic phase of insulin secretion in response to a meal is unrelated to family history of type 2 diabetes. *PLoS ONE.* (2017) 12:1–7. doi: 10.1371/journal.pone.0173654
131. Toledo PL, Torkko JM, Müller A, Wegbrod C, Sönmez A, Solimena M, et al. ICA512 RESP18 homology domain is a protein-condensing factor and insulin fibrillation inhibitor. *J Biol Chem.* (2019) 294:8564–76. doi: 10.1074/jbc.RA119.007607
132. Silvola JMU, Saraste A, Laitinen I, Savisto N, Laine VJO, Heinonen SE, et al. Effects of age, diet, and type 2 diabetes on the development and FDG uptake of atherosclerotic plaques. *JACC Cardiovasc Imaging.* (2011) 4:1294–301. doi: 10.1016/j.jcmg.2011.07.009
133. Bohn B, Mönkemöller K, Hilgard D, Dost A, Schwab KO, Lilienthal E, et al. Oral contraception in adolescents with type 1 diabetes and its association with cardiovascular risk factors. A multicenter DPV study on 24,011 patients from Germany, Austria or Luxembourg. *Pediatr Diabetes.* (2018) 19:937–44. doi: 10.1111/pedi.12656
134. Wanner N, Vornweg J, Combes A, Wilson S, Plappert J, Rafflenbeul G, et al. DNA methyltransferase 1 controls nephron progenitor cell renewal and differentiation. *J Am Soc Nephrol.* (2019) 30:63–78. doi: 10.1681/ASN.2018070736
135. Rinschen MM, Hoppe A-K, Kohli P, Hagmann H, Bertsch S, Höhne M, et al. YAP-mediated mechanotransduction determines the podocyte's response to damage. *Sci Signal.* (2017) 10:1–16. doi: 10.1126/scisignal.aaf8165
136. Hurcombe JA, Hartley P, Lay AC, Ni L, Bedford JJ, Leader JP, et al. Podocyte GSK3 is an evolutionarily conserved critical regulator of kidney function. *Nat Commun.* (2019) 10:403. doi: 10.1038/s41467-018-08235-1
137. Schell C, Rogg M, Suhm M, Helmstädter M, Sellung D, Yasuda-Yamahara M, et al. The FERM protein EPB41L5 regulates actomyosin contractility and focal adhesion formation to maintain the kidney filtration barrier. *Proc Natl Acad Sci.* (2017) 114:E4621–30. doi: 10.1073/pnas.1617004114
138. Lay AC, Hurcombe JA, Betin VMS, Barrington F, Rollason R, Ni L, et al. Prolonged exposure of mouse and human podocytes to insulin induces insulin resistance through lysosomal and proteasomal degradation of the insulin receptor. *Diabetologia.* (2017) 60:2299–311. doi: 10.1007/s00125-017-4394-0
139. Nead KT, Sharp SJ, Thompson DJ, Painter JN, Savage DB, Semple RK, et al. Evidence of a causal association between insulinemia and endometrial cancer: a mendelian randomization analysis. *J Natl Cancer Inst.* (2015) 107:1–7. doi: 10.1093/jnci/djv178
140. Lovestone S, Smith U. Advanced glycation end products, dementia, and diabetes. *Proc Natl Acad Sci.* (2014) 111:4743–4. doi: 10.1073/pnas.1402277111
141. Katrina Loomis A, Kabadi S, Preiss D, Hyde C, Bonato V, Louis MS, et al. Body mass index and risk of nonalcoholic fatty liver disease: two electronic health record prospective studies. *J Clin Endocrinol Metab.* (2016) 101:945–52. doi: 10.1210/jc.2015-3444
142. Lallukka S, Yki-Järvinen H. Non-alcoholic fatty liver disease and risk of type 2 diabetes. *Best Pract Res Clin Endocrinol Metab.* (2016) 30:385–95. doi: 10.1016/j.beem.2016.06.006
143. Franzini M, Musetti V, Guarino D, Caponi L, Paolicchi A, Emdin M, et al. γ-glutamyltransferase fractions in obese subjects with type 2 diabetes: relation to insulin sensitivity and effects of bariatric surgery. *Obes Surg.* (2018) 28:1363–71. doi: 10.1007/s11695-017-3017-7
144. StemBANCC. *IMI1 Final Project Report Public Summary - Stem cells for Biological Assays of Novel drugs and prediCtive toxiCology (StemBANCC).* StemBANCC (2018).
145. Avior Y, Sagi I, Benvenisty N. Pluripotent stem cells in disease modelling and drug discovery. *Nat Rev Mol Cell Biol.* (2016) 17:170–82. doi: 10.1038/nrm.2015.27
146. EBiSC. *The European Bank for induced Pluripotent Stem Cells Operated through The European Collection of Authenticated Cell Cultures.* EBiSC (2017).
147. Potter J. *Executive Summary of the Final Project Report - European Bank for Induced Pluripotent Stem Cells (EBISC).* EBiSC (2018).
148. Thurner M, Shenhav L, Wesolowska-Andersen A, Bennett AJ, Barrett A, Gloyn AL, et al. Genes associated with pancreas development and function maintain open chromatin in iPSCs generated from human pancreatic beta cells. *Stem Cell Rep.* (2017) 9:1395–405. doi: 10.1016/j.stemcr.2017.09.020
149. Khamis A, Canouil M, Siddiq A, Crouch H, Falchi M, Bulow M von, et al. Laser capture microdissection of human pancreatic islets reveals novel eQTLs associated with type 2 diabetes. *Mol Metab.* (2019) 24:98–107. doi: 10.1016/j.molmet.2019.03.004
150. Bunt M, Lako M, Barrett A, Gloyn AL, Hansson M, McCarthy MI, et al. Insights into islet development and biology through characterization of a human iPSC-derived endocrine pancreas model. *Islets.* (2016) 8:83–95. doi: 10.1080/19382014.2016.1182276
151. Martinez-Sanchez A, Nguyen-Tu MS, Leclerc I, Rutter GA. Manipulation and measurement of AMPK activity in pancreatic islets. *Methods Mol Biol.* (2018) 1732:413–31. doi: 10.1007/978-1-4939-7598-3_26
152. Heinonen SE, Genové G, Bengtsson E, Hübschle T, Åkesson L, Hiss K, et al. Animal models of diabetic macrovascular complications: Key players in the development of new therapeutic approaches. *J Diabetes Res.* (2015) 2015:404085. doi: 10.1155/2015/404085
153. Engelbertsen D, To F, Dunér P, Kotova O, Söderberg I, Alm R, et al. Increased inflammation in atherosclerotic lesions of diabetic akita-LDLr -/- mice compared to nondiabetic LDLr -/- mice. *Exp Diabetes Res.* (2012) 2012:176162. doi: 10.1155/2012/176162
154. Helmstädter M, Huber TB, Hermle T. Using the drosophila nephrocyte to model podocyte function and disease. *Front Pediatr.* (2017) 5:262. doi: 10.3389/fped.2017.00262
155. Mulder S, Hamidi H, Kretzler M, Ju W. An integrative systems biology approach for precision medicine in diabetic kidney disease. *Diabetes Obes Metab.* (2018) 20:6–13. doi: 10.1111/dom.13416
156. Atabaki-Pasdar N, Ohlsson M, Shungin D, Kurbasic A, Ingelsson E, Pearson ER, et al. Statistical power considerations in genotype-based recall randomized controlled trials. *Sci Rep.* (2016) 6:37307. doi: 10.1038/srep37307
157. Zeeuw D, Heerspink HJL, Jardine M, Perkovic V. Renal trials in diabetes need a platform : time for a global approach? *LANCET Diabetes Endocrinol.* (2017) 8587:2–4. doi: 10.1016/S2213-8587(17)30263-2
158. Heerspink HJL, List J, Perkovic V. New clinical trial designs for establishing drug efficacy and safety in a precision medicine era. *Diabetes Obes Metab.* (2018) 20:14–8. doi: 10.1111/dom.13417
159. Koivula RW, Heggie A, Barnett A, Cederberg H, Hansen TH, Koopman AD, et al. Discovery of biomarkers for glycaemic deterioration before and after the onset of type 2 diabetes: rationale and design of the epidemiological studies within the IMI DIRECT Consortium. *Diabetologia.* (2014) 57:1132–42. doi: 10.1007/s00125-014-3216-x
160. Rauh SP, Heymans MW, Koopman ADM, Nijpels G, Stehouwer CD, Thorand B, et al. Predicting glycated hemoglobin levels in the non-diabetic general population: Development and validation of the DIRECT-DETECT prediction model-a DIRECT study. *PLoS ONE.* (2017) 12:1–13. doi: 10.1371/journal.pone.0171816

161. Zetterqvist AV, Berglund LM, Blanco F, Garcia-vaz E, Wigren M, Dune P, et al. Inhibition of Nuclear Factor of Activated T-Cells (NFAT) suppresses accelerated atherosclerosis in diabetic mice. *PLoS ONE.* (2013) 8:e65020. doi: 10.1371/journal.pone.0065020
162. Perco P, Pena M, Heerspink HJL, Mayer G. Multimarker panels in diabetic kidney disease: the way to improved clinical trial design and clinical practice? *Kidney Int Rep.* (2019) 4:212–21. doi: 10.1016/j.ekir.2018.12.001
163. Zschiedrich S, Bork T, Liang W, Wanner N, Eulenbruch K, Munder S, et al. Targeting mTOR signaling can prevent the progression of FSGS. *J Am Soc Nephrol.* (2017) 28:2144–57. doi: 10.1681/ASN.2016050519
164. Garner KL, Betin VMS, Pinto V, Graham M, Abgueguen E, Barnes M, et al. Enhanced insulin receptor, but not PI3K, signalling protects podocytes from ER stress. *Sci Rep.* (2018) 8:1–13. doi: 10.1038/s41598-018-22233-9
165. Montastier E, Déjean S, Le Gall C, Saris WHM, Langin D, Viguerie N. Adipose tissue CIDEA is associated, independently of weight variation, to change in insulin resistance during a longitudinal weight control dietary program in obese individuals. *PLoS ONE.* (2014) 9:e98707. doi: 10.1371/journal.pone.0098707
166. Baltrusch S, Schmitt H, Brix A, Langer S, Lenzen S. Additive activation of glucokinase by the bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase and the chemical activator LY2121260. *Biochem Pharmacol.* (2012) 83:1300–6. doi: 10.1016/j.bcp.2012.01.020
167. Thorel F, Damond N, Chera S, Wiederkehr A, Thorens B, Meda P, et al. Normal glucagon signaling and β-cell function after near-total α-cell ablation in adult mice. *Diabetes.* (2011) 60:2872–82. doi: 10.2337/db11-0876
168. Friedman-Mazursky O, Elkon R, Efrat S. Redifferentiation of expanded human islet β cells by inhibition of ARX. *Sci Rep.* (2016) 6:1–11. doi: 10.1038/srep20698
169. Rachdi L, Kariawasam D, Aiëllo V, Herault Y, Janel N, Delabar JM, et al. Dyrk1A induces pancreatic β cell mass expansion and improves glucose tolerance. *Cell Cycle.* (2014) 13:2222–30. doi: 10.4161/cc.29250
170. Oshima M, Knoch K-P, Diedisheim M, Petzold A, Cattan P, Bugliani M, et al. Virus-like infection induces human β cell dedifferentiation. *JCI Insight.* (2018) 3:1–17. doi: 10.1172/jci.insight.97732
171. Hakonen E, Chandra V, Fogarty CL, Yu NYL, Ustinov J, Katayama S, et al. MANF protects human pancreatic beta cells against stress-induced cell death. *Diabetologia.* (2018) 61:2202–14. doi: 10.1007/s00125-018-4687-y
172. Buitinga M, Jansen T, van der Kroon I, Woliner-van der Weg W, Boss M, Janssen M, et al. Succinylated gelatin improves the theranostic potential of radiolabeled exendin-4 in insulinoma patients. *J Nucl Med.* (2019) 60:812–6. doi: 10.2967/jnumed.118.219980
173. Cosentino C, Cnop M, Igoillo-Esteve M. The tRNA epitranscriptome and diabetes: emergence of tRNA hypomodifications as a cause of pancreatic β-cell failure. *Endocrinology.* (2019) 160:1262–74. doi: 10.1210/en.2019-00098
174. Nathan G, Kredo-Russo S, Geiger T, Lenz A, Kaspi H, Hornstein E, et al. MiR-375 promotes redifferentiation of adult human β cells expanded *in vitro*. *PLoS ONE.* (2015) 10:1–18. doi: 10.1371/journal.pone.0122108
175. Bénardeau A, Verry P, Atzpodien EA, Funk JM, Meyer M, Mizrahi J, et al. Effects of the dual PPAR-α/γ agonist aleglitazar on glycaemic control and organ protection in the Zucker diabetic fatty rat. *Diabetes Obes Metab.* (2013) 15:164–74. doi: 10.1111/dom.12006
176. Gonçalves I, Edsfeldt A, Colhoun HM, Shore AC, Palombo C, Natali A, et al. Association between renin and atherosclerotic burden in subjects with and without type 2 diabetes. *BMC Cardiovasc Disord.* (2016) 16:1–10. doi: 10.1186/s12872-016-0346-8
177. Patrono C. Low-dose aspirin in primary prevention: cardioprotection, chemoprevention, both, or neither? *Eur Heart J.* (2013) 34:3403–11. doi: 10.1093/eurheartj/eht058
178. Preiss D, Dawed A, Welsh P, Heggie A, Jones AG, Dekker J, et al. Sustained influence of metformin therapy on circulating glucagon-like peptide-1 levels in individuals with and without type 2 diabetes. *Diabetes Obes Metab.* (2017) 19:356–63. doi: 10.1111/dom.12826
179. Breyer MD, Kretzler M. Novel avenues for drug discovery in diabetic kidney disease. *Expert Opin Drug Discov.* (2018) 13:65–74. doi: 10.1080/17460441.2018.1398731
180. Heerspink HJL, Perco P, Mulder S, Leierer J, Hansen MK, Heinzel A, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. *Diabetologia.* (2019) 62:1154–66. doi: 10.1007/s00125-019-4859-4
181. Davies JA, Chang C-H, Lawrence ML, Mills CG, Mullins JJ. Engineered kidneys: principles, progress, and prospects. *Adv Regen Biol.* (2014) 1:24990. doi: 10.3402/arb.v1.24990
182. Davies JA, Chang CH. Engineering kidneys from simple cell suspensions: an exercise in self-organization. *Pediatr Nephrol.* (2014) 29:519–24. doi: 10.1007/s00467-013-2579-4
183. Davies J. Engineered renal tissue as a potential platform for pharmacokinetic and nephrotoxicity testing. *Drug Discov Today.* (2014) 19:725–9. doi: 10.1016/j.drudis.2013.10.023
184. Massai D, Bolesani E, Diaz DR, Kropp C, Kempf H, Halloin C, et al. Sensitivity of human pluripotent stem cells to insulin precipitation induced by peristaltic pump-based medium circulation: Considerations on process development. *Sci Rep.* (2017) 7:1–15. doi: 10.1038/s41598-017-04158-x
185. McCarthy MI. Painting a new picture of personalised medicine for diabetes. *Diabetologia.* (2017) 60:793–9. doi: 10.1007/s00125-017-4210-x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 06 July 2021
doi: 10.3389/fmed.2021.686165

Patient Preferences for Multiple Myeloma Treatments: A Multinational Qualitative Study

Rosanne Janssens[1], Tamika Lang[2], Ana Vallejo[2], Jayne Galinsky[2], Ananda Plate[2], Kate Morgan[2], Elena Cabezudo[3], Raija Silvennoinen[4,5], Daniel Coriu[6,7], Sorina Badelita[7], Ruxandra Irimia[6,7], Minna Anttonen[8], Riikka-Leena Manninen[8], Elise Schoefs[1], Martina Vandebroek[9], Anneleen Vanhellemont[10], Michel Delforge[10], Hilde Stevens[11], Steven Simoens[1] and Isabelle Huys[1]*

[1] Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [2] Myeloma Patients Europe, Brussels, Belgium, [3] Department of Haematology, H. Moises Broggi/ICO-Hospitalet, Barcelona, Spain, [4] Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland, [5] University of Helsinki, Helsinki, Finland, [6] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [7] Fundeni Clinical Institute, Bucharest, Romania, [8] Association of Cancer Patients in Finland, Helsinki, Finland, [9] Faculty of Economics and Business, KU Leuven, Leuven, Belgium, [10] University Hospital Leuven, Leuven, Belgium, [11] Institute for Interdisciplinary Innovation in Healthcare (I3h), Université Libre de Bruxelles (ULB), Brussels, Belgium

OPEN ACCESS

Edited by:
Bruno Sepodes,
University of Lisbon, Portugal

Reviewed by:
Dinah Duarte,
Infarmed, Autoridade Nacional do Medicamento e Produtos de Saúde, I. P., Portugal
Segundo Mariz,
European Medicines Agency, Netherlands
Virginie Hivert,
European Organisation for Rare Diseases (EURORDIS), France

***Correspondence:**
Rosanne Janssens
rosanne.janssens@kuleuven.be

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: 26 March 2021
Accepted: 28 May 2021
Published: 06 July 2021

Citation:
Janssens R, Lang T, Vallejo A, Galinsky J, Plate A, Morgan K, Cabezudo E, Silvennoinen R, Coriu D, Badelita S, Irimia R, Anttonen M, Manninen R-L, Schoefs E, Vandebroek M, Vanhellemont A, Delforge M, Stevens H, Simoens S and Huys I (2021) Patient Preferences for Multiple Myeloma Treatments: A Multinational Qualitative Study. Front. Med. 8:686165. doi: 10.3389/fmed.2021.686165

Background: Investigational and marketed drugs for the treatment of multiple myeloma (MM) are associated with a range of characteristics and uncertainties regarding long term side-effects and efficacy. This raises questions about what matters most to patients living with this disease. This study aimed to understand which characteristics MM patients find most important, and hence should be included as attributes and levels in a subsequent quantitative preference survey among MM patients.

Methods: This qualitative study involved: (i) a scoping literature review, (ii) discussions with MM patients ($n = 24$) in Belgium, Finland, Romania, and Spain using *Nominal Group Technique,* (iii) a qualitative thematic analysis including multi-stakeholder discussions.

Results: MM patients voiced significant expectations and hopes that treatments would extend their lives and reduce their cancer signs and symptoms. Participants however raised concerns about life-threatening side-effects that could cause permanent organ damage. Bone fractures and debilitating neuropathic effects (such as chronic tingling sensations) were highlighted as major issues reducing patients' independence and mobility. Patients discussed the negative impact of the following symptoms and side-effects on their daily activities: thinking problems, increased susceptibility to infections, reduced energy, pain, emotional problems, and vision problems. MM patients were concerned with uncertainties regarding the durability of positive treatment outcomes, and the cause, severity, and duration of their symptoms and side-effects. Patients feared short-term positive treatment responses complicated by permanent, severe side-effects and symptoms.

Conclusions: This study gained an in-depth understanding of the treatment and disease-related characteristics and types of attribute levels (severity, duration) that are most important to MM patients. Results from this study argue in favor of MM

drug development and individual treatment decision-making that focuses not only on extending patients' lives but also on addressing those symptoms and side-effects that significantly impact MM patients' quality of life. This study underscores a need for transparent communication toward MM patients about MM treatment outcomes and uncertainties regarding their long-term efficacy and safety. Finally, this study may help drug developers and decision-makers understand which treatment outcomes and uncertainties are most important to MM patients and therefore should be incorporated in MM drug development, evaluation, and clinical practice.

Keywords: multiple myeloma, patient preferences, nominal group technique, qualitative research, attributes, drug development, regulatory benefit-risk assessment, health technology assessment

INTRODUCTION

Patient preference studies use qualitative and quantitative methods to understand which treatment and disease-related characteristics (efficacy outcomes, side-effects, and symptoms) are important to patients, how important they are to patients, the trade-offs patients are willing to make between these characteristics, and how preferences may vary according to individual patient characteristics (1–3). Stakeholders involved in drug development and evaluation—such as drug developers, regulators, *Health Technology Assessment* (HTA) bodies and payers—have acknowledged the potential value of using patient preference studies to inform their respective decisions (4–6). More specifically, patient preference studies could: (i) reveal the patient perspective on unmet treatment needs in early drug development, (ii) inform the development of patient reported outcome measures and the selection of clinical trial endpoints, (iii) help understand which are the key favorable and unfavorable effects and uncertainties in regulatory benefit-risk assessment, (iv) quantify the relative importance of treatment characteristics in HTA and payer decisions, and (v) inform the development of decision aids used in shared individual treatment decision-making between patients and clinicians (1, 4–18).

On the regulatory level, the *European Medicines Agency* (EMA) and the *US Food and Drug Administration* (FDA) intend to systematically include preference studies in regulatory benefit-risk assessment (4–6, 19–21). Mirroring the FDA's efforts toward guidance surrounding patient preference studies, the EMA aims to develop guidance on appropriate methods for patient preference study design, conduct, analysis, and presentation for regulatory purposes, to ensure that high quality methodologies are applied (4). A reflection paper by the EMA details opportunities for the development of new guidelines by the *International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use* (ICH). These guidelines will aim to provide a globally harmonized approach to inclusion of the patient's perspective in a way that is methodologically sound and sustainable for both regulated industry and regulatory authorities (22). From the HTA/reimbursement perspective, the *National Institute for Health and Care Excellence* (NICE) argues that patient preference studies could be used to inform the selection of clinical trial endpoints, and inform regulatory benefit-risk assessment, echoing the EMA's viewpoints (23). In addition, NICE sees a role in preference studies for informing their HTA assessment alongside other types of clinical and economic evidence (23, 24). Similarly, drug developers more often include preference studies in their drug development plans, regulatory, and HTA submissions (25).

However, while stakeholders have expressed an interest in using patient preference studies to inform their respective decisions, previous research has revealed that more evidence-based preference study development is needed to build methodological and practical knowledge and address uncertainties regarding the design, conduct, and use of patient preference studies (1, 10, 26). In response to this, several research projects, such as the IMI PREFER project, have been initiated by drug developers, academic researchers, as well as HTA bodies and regulatory agencies. Such projects aim to investigate how patient preference studies could inform decision-making, and how such studies could be designed to meet methodological requirements of stakeholders involved in these decisions (27–29).

A crucial initial step in patient preference studies is the use of qualitative data collection for identification of the key attributes and levels of importance to patients for inclusion in the subsequent quantitative phase of the study. Attributes are the key aspects that impact patients' choices toward treatments and include benefits, risks or other clinical and non-clinical aspects that influence the desirability or acceptability of medical interventions (30). Therefore, attributes of key importance to patients may align decision-making with patient's perspectives both in the individual treatment decision-making context (16–18), as well as in decision-making regarding drug development, authorization, and reimbursement. Attribute levels are the values or categories used to characterize the performance of a treatment (31). As qualitative methods provide in-depth and meaningful information from patients, their use is recommended for the development of attributes and levels. Qualitative methods with patients may reduce the potential for misspecification of attributes through overreliance on the views of experts and researchers (27, 28). In doing so, using qualitative research for the development of attributes and levels may improve the validity of subsequent quantitative preference surveys. Therefore, by combining both qualitative and quantitative

methods in preference studies, the data collected on patient preferences is likely to be more comprehensive, meaningful, and a valid interpretation of the true patient perspective (32). However, qualitative preference research that informs subsequent preference surveys remains underreported, creating uncertainty regarding the methodological and practical application of these methods and results for informing subsequent quantitative preference surveys.

Eliciting preferences from *Multiple Myeloma* (MM) patients is especially valuable in view of the rapid development of various novel MM treatments with substantial effects on survival, toxicity, efficacy, and related long-term uncertainties. Among patients and various stakeholders, the impact of these treatments on patients' lives, attitudes and choices toward treatments is largely unknown. MM is the second most frequent hematological malignancy after non-Hodgkin lymphoma, accounting for 1% of all cancers and 10% of blood cancers (33, 34). MM is characterized by a proliferation of plasma cells in the bone marrow, typically accompanied by the secretion of monoclonal immunoglobulins (M-proteins or paraproteins) (35). This proliferation causes symptoms such as skeletal damage, hypercalcemia, renal insufficiency, anemia, and infections (36). Because MM disrupts the normal functioning of the bone marrow, damages the bones and causes kidney failure, MM is considered to be a debilitating and life-threatening disease. Despite several drugs being available, MM has been labeled an incurable disease and only half of the diagnosed patients live longer than 5 years (33).

New MM treatments are currently being developed that have different side-effect profiles, mechanism of action, and efficacy from those currently available. More specifically, innovative treatments currently under development, such as bispecific T-cell engagers and chimeric antigen receptor therapies (CAR-T), have shown to be efficacious but also associated with severe risks such as cytokine release syndrome (an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction) and neurotoxicity's (such as encephalopathy, aphasia, delirium, tremor, and seizures) (37). Differences between treatments, based on varying benefits and risks, raise the question about how MM patients value these treatment aspects. Furthermore, decisions surrounding MM treatment can be labeled as "preference sensitive" decisions where: (i) multiple treatment options exist and there is no option that is clearly superior for all patients; (ii) the evidence supporting one option over others is considerably uncertain or variable and (iii) patients' views about the most important benefits and acceptable risks of a treatment vary considerably within a population and may differ from those of healthcare professionals (20).

Therefore, given the lack of valid, meaningful, and comprehensive qualitative research on MM patient preferences, the present study aimed to understand which characteristics MM patients find most important, and hence should be included as attributes and attribute levels in a subsequent preference survey. By pursuing these objectives, this study derives experience-based learnings regarding the design, conduct and analysis of qualitative research aiming to develop attributes and levels for inclusion in subsequent preference surveys in the context of drug development and evaluation. Such methodological learnings may foster the development of a standardized approach to be used by all stakeholders across disease areas, and serve to include a validated patient preference framework for drug development, allowing for future comparisons of patient preference studies and their results.

MATERIALS AND METHODS

Study Context

The *Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle* (PREFER) project is a 6-year public private partnership that received funding from the *Innovative Medicines Initiative* (IMI) 2. This project seeks to guide drug developers, regulatory authorities, and HTA bodies (including reimbursement agencies and payers) on how and when patient preference studies should be performed and how the results can be used to inform decision-making. The initial phase of the PREFER project included discussions with a broad representation of stakeholders such as patients, patient organizations, regulatory authorities, HTA bodies, and reimbursement agencies that expressed interest in preference studies, and revealed the need to further explore and test preference methods (1, 7, 9, 10, 26). Therefore, this study has been developed in the context of recommendations formulated by IMI PREFER. The results of PREFER are expected to lead to changed practices, in that stakeholders will routinely assess whether a preference study would add value at key decision points in the medicinal product life cycle and, if so, implement patient preference studies according to the PREFER project recommendations (38).

Study Design

This study was designed and executed according to: (i) the recommendations on qualitative data collection and analysis methods for initial attribute development (39, 40); (ii) the steps describing attribute and level development in health preference research formulated by Bridges et al. (41); (iii) the criteria described by Hensher et al. (42) regarding what constitutes "good" attributes; (iv) the framework method for thematic analysis described by Lacey and Luff (43) and (v) the recommendations for reporting the results of a qualitative preference study (40).

Following recommendations by Hollin et al. (40), Coast et al. (39), and Bridges et al. (41), this paper describes: (i) the rationale for the methodological steps and choices taken to develop attributes and levels; (ii) a detailed description of the included participants; (iii) details regarding the practical steps and setting of the qualitative study including the recruitment, discussion guides, involved researchers; (iv) details of the subsequent steps including the transcription, translation, and analysis and (v) the results of the qualitative study.

Study Phases

To understand the key characteristics of importance to MM patients, a qualitative study was completed in three phases (**Figure 1**). Several preference studies attest to the usefulness of

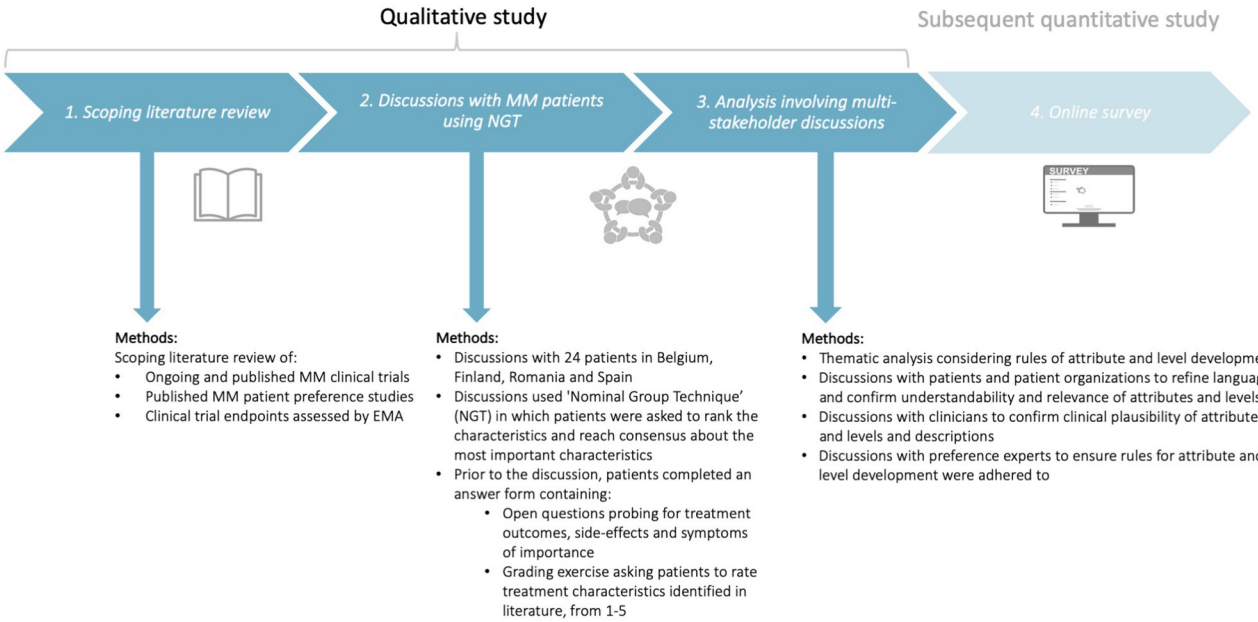


FIGURE 1 | Design of the qualitative study consisting of three phases: (i) a scoping literature review, (ii) discussions with MM patients using Nominal Group Technique (NGT), and (iii) analysis involving multi-stakeholder discussions with patients, patient organizations, clinicians, and preference experts. The subsequent quantitative study will be conducted using the attributes and levels identified in the present qualitative study. MM, Multiple Myeloma; NGT, Nominal Group Technique; EMA, European Medicines Agency.

qualitative methods with patients and advocate for the use of literature reviews to inform the development of attributes and levels (31, 39–41, 44). Therefore, this study involved three phases, whereby each phase informed the subsequent phase (**Figure 1**): (i) a scoping literature review, (ii) discussions with MM patients using *Nominal Group Technique* (NGT), and (iii) a combined quantitative and qualitative thematic analysis involving multi-stakeholder discussions with patients, patient organizations, clinicians, and preference research experts.

Phase 1: Scoping Literature Review

The scoping review aimed to identify potential relevant characteristics (treatment outcomes, symptoms, and side-effects) for grading in subsequent patient discussions using NGT. Bridges et al. (41) recommend that attribute development should be supported by evidence on the potential range of preferences and values that respondents of the preference survey may hold. Therefore, the list of treatment characteristics that was used for the NGT (**Appendix 1**, section 3) was informed by a scoping literature review of: (i) the attributes and key results of published preference studies conducted among MM patients (**Appendices 2**, **3**), (ii) favorable and unfavorable effects of MM treatments already assessed by EMA that includes characteristics of treatments already being prescribed to patients (**Appendices 4**, **5**) and (iii) primary and secondary endpoints and adverse events reported in phase 3 MM clinical trials in the European Union (EU) to ensure the attribute list captured treatment characteristics of therapies in development; this was done so that in the discussions patients would be able to discuss potential "future" treatment outcomes and side-effects, even though they had not yet experienced them (**Appendices 6**, **7**).

Searches for published preference studies among MM patients were conducted in PubMed and Embase (see **Appendix 2** for the selection procedure). The search queries included free text terms in title and/or abstract and *Medical Subject Headings* (MeSH) and included synonyms for the following two concepts: "multiple myeloma" AND "patient preferences." The database searches yielded 250 publications. Publications were included if they reported preferences from MM patients. Conversely, studies were excluded if: (i) preferences were not elicited from patients (e.g., only from caregivers or clinicians); (ii) no preference method (qualitative/quantitative) was applied; (iii) no preferences were reported (e.g., study protocols) and (iv) the study focused on: patient preferences for whether or not patients are willing to participate in decision-making, patient preferences for remote monitoring, or if the study investigated whether patients do or do not want to receive information. The results were screened in a 2-fold manner. First, the title and abstract were screened based on the in- and exclusion criteria. Afterwards, the full text was reviewed against the same criteria. From the database searches, 15 publications were included in the review. Subsequently, the following information was extracted (**Appendix 2**): (i) first author and year; (ii) type of publication; (iii) research objective; (iv) participants; (v) preference method(s) used; (v) attributes/items/factors identified or used in the study and (vi) key results. To develop a final list of characteristics for grading (**Appendix 1**), the treatment characteristics that emerged from the scoping review were combined and then grouped with

both the characteristics of treatments being prescribed to patients (**Appendices 4**, **5**) and with the characteristics of treatments included in phase 3 MM clinical trials (**Appendices 6**, **7**).

Phase 2: Discussions With Multiple Myeloma Patients Using Nominal Group Technique

Objectives and Rationale

Phase 2 aimed to: (i) understand which characteristics, including those identified in phase 1, were most important to MM patients, and hence should be included as attributes in the subsequent preference survey that quantifies the relative importance of these attributes; (ii) understand the factors and dimensions influencing patient choices; what determines whether patients would take, not take, or discontinue a certain treatment, and hence should be included as attribute levels and (iii) understand the language patients use to describe symptoms, treatment outcomes, and side-effects, and hence should be the language used to describe the attributes and levels.

To reach these objectives, discussions with 24 MM patients in Belgium, Finland, Romania, and Spain were held (see "Recruitment, study population, and setting" for a rationale for including these countries). The discussions used NGT, a type of focus group discussion methodology, that asked patients to rank and reach consensus on the most important characteristics (see "step-by-step procedures"). While standard focus group discussions use open discussion throughout, NGT is a consensus focus group methodology that differs from standard focus group discussions. In addition to providing a format for open discussion, NGT includes a structured four-stage process and a methodology for capturing participant responses and with inclusion of prioritization and participant's individual and collective perspectives. NGT is specifically suited to identify attributes due to its structured approach and grading methodology; the grading allows researchers to select and understand which treatment characteristics are most important and hence should be used for developing the attributes in the subsequent preference survey. Furthermore, NGT has the advantage over other qualitative consensus methods as it ensures groups to reach consensus in a short period of time (39).

Patient Involvement and Piloting

In addition to inclusion in NGT discussions, MM patients, and MM patient organizations were involved in all steps of research. MM patients and/or MM patient organization members provided written and oral feedback on all patient materials including the information sheet, informed consent, answer sheet (including explanatory parts), and questions. All patient documents were first translated by a professional translation company to the native language of participants, and subsequently revised for accuracy and understandability by patients, patient organizations, and clinicians.

Recruitment, Study Population, and Setting

Hematologists performed the recruitment at their respective hospitals and were asked to ensure a diverse patient population was invited to participate in the discussions. It was anticipated that several individual patient characteristics—such as socio-demographics, disease stage and treatment experience—could influence participants' opinions and rankings. The goal was to ensure that the attributes and levels identified in this study were not directed only to patients with a specific treatment exposure, disease history, age or country of origin; but rather toward all patients along the MM spectrum. Therefore, during recruitment, heterogeneity in terms of treatment experience, disease stage, age, and country was introduced as much as possible. During sampling, hematologists used the following inclusion criteria: (i) patients diagnosed with symptomatic MM; (ii) patients ability to understand the language to be used in the discussion and (iii) patients ability to participate in the discussion.

Recruitment sought to include between 5 and 7 MM patients across four countries: Belgium, Finland, Romania, and Spain. These countries were included to account for potential differences in patient characteristics and, as mentioned above, to increase heterogeneity and thereby ensure the identified attributes and levels were not only relevant to a particular type of patient. While McMillan et al. (45) describes that most NGTs include between 2 and 14 participants, a maximum of seven is recommended as a much larger number would delay the phased process of the NGT discussion, which aims to reach consensus in a short time span (up to 2 h). Therefore, minimally 5 and maximally 7 patients were included in each country. There are no guidelines that define how much data, and hence, participants should be included in qualitative research (30). Instead, saturation is often used to define when data collection can stop (30, 32, 46). Saturation is defined as the point when "*no new information or themes are observed in the data*" (47). Hennink et al. (48) state that when the goal is to identify "core" issues, few discussions could be enough to reach data saturation, and some studies have reached saturation after 4–6 focus groups (30, 32, 46). Since the goal of our study was to identify core, overarching attributes, it was expected that data saturation could be achieved by including between 5 and 7 MM patients in four countries ($n = 24$ across all countries). Following qualitative data collection, it appeared that the same themes of treatment attributes were observed across different countries. Hence, it was decided that saturation was reached and no additional data was needed to inform the attributes and levels.

The discussions were organized at a location convenient for participants, between April and November 2020, and considered the implications of the coronavirus (COVID-19) pandemic; discussions were organized either face-to-face or online, according to the preference of participants and recommendations set-out by hospitals regarding patient contact.

Step-by-Step Procedures

As part of the recruitment process, an invitation letter was sent to those expressing interest in the study and fulfilling inclusion criteria (see "Study recruitment, population and setting"). Potential participants were contacted to verify their willingness to participate and if so, arrange the practicalities of the discussion. The information sheet and informed consent was provided to participants in their own language. Both documents were provided to participants prior to the discussion, and the

informed consent form was signed by all participants before the discussion. As preparation for the discussion, participants were invited to complete an answer sheet containing three sections: (i) participants' background characteristics, including Chew's Set of Brief Screening Questions (**Appendix 1**, section 1); (ii) open questions probing for treatment characteristics of importance (**Appendix 1**, section 2) and (iii) a grading exercise asking patients to grade the treatment characteristics identified in the scoping literature review from 1 (= not important at all) to 5 (= very important) (**Appendix 1**, section 3). The NGT discussion consisted of the following four steps (**Appendix 8**): (i) idea, (ii) round robin, (iii) clarification and finalization of the list of attributes, (iv) grading and consensus.

Each discussion was conducted by a person fluent in the native language of the participants. The discussions lasted around 90 min, were voice-recorded and included a break of ∼10 min. The audio-recordings were transcribed verbatim by a professional transcribing company in the original language and then translated to English. To ensure patients' opinions were accurately reflected in the subsequent analysis and development of the attributes and levels, the moderators were closely involved in the subsequent analysis (see phase 3).

Phase 3: Analysis Involving Multi-Stakeholder Discussions

In the final phase, a combined quantitative descriptive analysis of patients' rankings and iterative qualitative thematic analysis of the discussion transcripts was used to determine overarching themes of prioritized treatment characteristics relevant to all participating patients, regardless of their treatment exposure, disease history, age, or country of origin.

Quantitative Analysis

Participants' self-reported characteristics, as obtained through sections 1 and 3 of the answer sheet (**Appendix 1**) were analyzed descriptively using Microsoft Excel. Patient characteristics were tabulated for all patients together and for each of the questions asked in **Appendix 1**. ANOVA and Fischer exact tests were performed to investigate statistically significant differences between groups of participants and countries. Health literacy was determined using Chews' set of brief screening questions (49). The grades for the characteristics were calculated per country to derive rank orders and averages at country level. To obtain a final rank of the themes pertaining to treatment characteristics, the averages for each theme were calculated by combining the previously calculated averages obtained in the four countries.

Qualitative Analysis

The qualitative analysis took into account the following criteria and best practices for attribute and level development; therefore, attributes and levels should be:

- Relevant to patients and/or policy-makers, plausible, capable of being traded, unambiguous, distinctly different from other included attributes, comprehensive, and of salience to respondent's decisions (39, 40);
- Inclusive of all aspects that might be important for an individual in coming to a decision (28, 39);
- Not too close to the latent construct such as overall quality of life (28);
- Not have such a large impact on decisions that large numbers of respondents of the quantitative survey make no errors when deciding, such as overall happiness with the alternative treatments presented in the preference survey (28);
- Not intrinsic to a person's personality, these aspects need to be considered in analyzing and describing preference heterogeneity (28);
- Developed through an iterative, constant comparative analysis approach to continually modify and extend the attributes and levels to ensure that all key aspects can be incorporated through this modification (28);
- Inclusive of all aspects that might be important for an individual in coming to a decision, as ignoring important attributes and levels may bias findings; and qualitative methods to determine overarching attributes must encompass key themes combined with piloting to avoid bias (28);
- Created through a process consisting of conceptual development where the attributes and levels are identified, followed by refinement of language to ensure the intended meaning is conveyed toward the participants in the preference survey (28);
- Inclusive of all characteristics that potentially characterize the alternative treatments presented to participants in the preference survey, with consideration that some characteristics may be excluded if the alternative treatments are not plausible to subjects (39).

The framework method by Lacey and Luff (43) was used to develop overarching themes that capture prioritized characteristics for inclusion as attributes and levels (**Table 1**). The analysis was performed by a multi-stakeholder team including patients, patient organizations, clinicians, and academic preference research experts. Discussions with patients and patient organizations specifically sought to confirm whether the themes captured the most relevant characteristics for inclusion as attributes and levels, and whether the results described accurately represented their views. In particular, MM patients and/or MM patient organization members provided written and oral feedback on the relevance, comprehensiveness, and understandability of the themes of characteristics for inclusion as attributes and levels. Discussions with clinicians were held to confirm the clinical plausibility of the attributes and levels. Also, to ensure adherence to rules for attribute and level development, preference expert input was included. Finally, the attributes and levels were reviewed by MM patients to receive end-user feedback.

RESULTS

Participants' Characteristics

In total, 24 MM patients (6 per country, 4 countries) agreed to participate. The average response rate across countries was 46%. Reasons for not participating were: (i) research topic was not in their field of interest; and (ii) not willing to communicate in groups. The mean age across countries varied between 60 and 65

TABLE 1 | Iterative steps of the qualitative thematic analysis using the framework method.

1. Familiarization	The transcripts were thoroughly read and re-read and the audio-recordings were listened to again if a certain part of the transcript was unclear. The margins of the transcripts were used to write down analytical notes, thoughts or impressions (e.g., when participants expressed exceptionally strong or contrasting views). Discussions among the moderators on preliminary findings sought to confirm whether they interpreted the discussions in the same manner.
2. Identifying a thematic framework	A list of overarching themes capturing prioritized treatment characteristics was developed based on the views expressed by patients during the discussions, in their answer sheet, and the ranked list of characteristics and explanations. This list was transported to NVivo (11th edition, QSR International) for coding.
3. Coding	Literal quotations (text) in the transcript and answer sheets were attached to each of the themes, describing what participants stated about these themes (coding). Throughout the coding process, it was assessed whether the list of themes and their explanations covered what participants said. If not, modifications were made to the name of the theme. Discussions among the team (see below) sought to modify and reach consensus about the themes. The end result was the final list of themes, each with a brief explanatory description of their meaning including examples to further explain the theme (see below).
4. Charting	NVivo was used for charting (summarizing) the data per attribute.
5. Mapping and interpretation	Several meetings among a multi-stakeholder team were organized to discuss the qualitative findings (the final list of themes) together with the characteristic scorings of the quantitative analysis. During these meetings, consensus was reached about the final list of attribute themes and associated levels to take forward to the quantitative survey.

An iterative, constant comparative analysis approach was used to allow for continuous modifications and extensions of the themes to ensure that all key aspects of importance to patients could be incorporated.

years (M: 61 across all countries, range 46–73). Most participants had a Masters' degree (42%) followed by a Bachelor (25%) or High school degree (25%). Most participants (58%) described their activity level as *"not my normal self, but able to be up and about with fairly normal activities" (fair mobility)*, followed by *"normal, without any limitations" (no limitations;* 25%) and 13% identified themselves as *"not feeling up to most of the things, but in bed of chair less than half of the day"* (sedentary) (**Appendix 9**). Most participants (88%) did not live alone at the time of the discussion. Many participants were employed (50%) or retired (42%). The median participant received their MM diagnosis at the age of 55. Participants were heterogeneous in terms of how long they had received their diagnosis; ranging between 18 years ago to the same year of the discussion.

Nearly all patients (96%) were on treatment at the time of the discussion. Across countries, participants were most frequently treated with proteasome inhibitors (PIs) (50%), immunomodulating agents (IMiDs) (46%) and steroids (46%), followed by supportive treatments (33%, e.g., calcium and vitamin D supplements, pain medication) and monoclonal antibodies (mAbs) (21%). Participants were previously treated with an average of three different regimens (one treatment line referring to one drug or a combination of drugs given for a specific time duration) at the time of the discussion and the number of treatment lines across participants ranged between one and seven previous treatment lines. Fifty-eight percentage of patients indicated that they suffer from at least one of the following chronic health problems: heart rhythm disorders, prostate hypertrophy, hypertension, hypothyroidism, glaucoma, renal insufficiency, diabetes, and arthritis. The vast majority (83%) of participants indicated that they were not in frequent contact with a patient organization. Across countries, the majority of participants had a high (46%) or moderate (42%) health literacy.

Statistical tests (Fischer exact and ANOVA) revealed no significant differences between the patient groups of the different countries, regarding their age ($F = 1.61$, $p = 0.22$), gender ($X^2 = 1.90$, $p = 0.81$), education ($X^2 = 8.01$, $p = 0.62$), work status ($X^2 = 10.76$, $p = 0.05$), contact with patient organizations ($X^2 = 3.72$, $p = 0.22$), other chronic health problems ($X^2 = 6.73$, $p = 0.08$), health literacy ($X^2 = 2.99$, $p = 0.93$), and number of treatment lines ($F = 2.64$, $p = 0.09$).

However, there were statistical differences in activity level ($X^2 = 10.78$, $p = 0.03$), living situation ($X^2 = 4.70$, $p = 0.04$), enrolment in clinical trial ($X^2 = 8.33$, $p = 0.04$), and years since diagnosis ($F = 3.28$, $p = 0.04$). In particular, the Finnish group had a better activity level than the other groups; 67% of the participants considered their activity level as *"normal, without any limitations."* Further, only 50% of the Finish group was not living alone vs. 100% in the other countries. Regarding clinical trial enrolment, nearly all Finnish participants were currently (50%) or previously (30%) enrolled in a clinical trial, as opposed to the other countries, where nearly equal distributions were observed (42% yes vs. 54% no). Spanish participants were more recently diagnosed with MM (M: 1 year since diagnosis) vs. Belgian participants (M: 9 years) (see **Appendix 9** for a full overview of participants' characteristics).

Themes Capturing Prioritized Characteristics for Inclusion in Attributes and Levels

Patients across countries and with varying disease and treatment experiences reached consensus on the importance of the following eleven attribute themes (outcomes, side-effects, and symptoms): life expectancy, life-threatening side-effects, treatment response, mobility problems, thinking problems, infections, reduced energy, pain, emotional problems, eating and digestive problems, and vision problems. These attribute

themes are categorized below into: (i) favorable effects: treatment outcomes considered desirable or beneficial, and (ii) unfavorable effects: side-effects and symptoms negatively impacting patients' life expectancy and/or quality of life.

Regarding the types of attribute levels, patients highlighted the importance of specifying the duration and severity of the treatment effects as it would determine their treatment choices. In particular, patients expressed the fear of short-term positive treatment outcomes and long-term negative effects. Conversely, several expressed that transient side-effect are more acceptable. Patients were also afraid of symptoms and side-effects that are so severe, in that sense that they would hamper them in performing their daily activities. Therefore, severity and duration were specified as attribute levels.

Patients highlighted the importance of both life expectancy and quality of life: *"as many years with the best quality of life as possible*" and highlighted that the balance between the treatments' effect on their life expectancy and quality (would) determine their individual treatment choices: *"I would reconsider continuing treatment) if the impact on daily life is so great that the quantity of life (years) becomes less important than the quality of life."* Participants' willingness to accept a reduction in quality of life in return for an increased life expectancy differed across participants and depended on their individual situation and personal attitudes. In particular, participants who were older, had undergone more treatments, and had no young children, seemed to place more importance on quality of life related attributes (such as pain) rather than life expectancy, and vice versa. However, on average, life expectancy was graded the highest by MM patients, followed by side-effects and symptoms that significantly impact patients' life expectancy and/or quality of life.

Favorable Effects: Treatment Outcomes Considered Desirable or Beneficial

Life Expectancy

Increasing life expectancy was on average, the most important treatment outcome for patients across the four countries: *"Lengthened life span is of course most important," "I think that the most desirable effect of myeloma treatment would be longer life, and, I don't know whether this needs any justification as to why."* Depending on their personal context, participants described that they want to be there to see their children grow up, take care of their loved ones and be professionally active. MM patients described the negative psychological impact of the uncertainty of how long they had to live: *"the sword of Damocles hanging over me."*

Treatment Response

Participants voiced significant expectations and hopes that treatments would work to successfully fight their cancer and extend their lives. Any improvement or positive treatment outcome was considered to be important: *"Any improvement would be welcome."* Participants agreed that they want a treatment that will have lasting improvements in any signs and symptoms associated with their cancer and removal of cancer cells.

Many patients hoped for a complete remission, i.e., a complete removal of all cancer signs. Several participants acknowledged that cure—a complete and permanent elimination of all cancer cells—is not achievable with current treatments. However, to be cured permanently, was considered to be the ultimate treatment goal by some patients: *"I am hoping that by continuing the treatment I will get cured."* Several also described that if the treatment would cure them, they would be willing to accept even those treatment side-effects that they had described as the worst treatment effects.

Positive laboratory and imaging tests were recognized as important indicators of a stabilization of cancer progression. The knowledge and interest of some participants regarding MM biomarkers was remarkable; several participants shared detailed experiences regarding their test results and the importance of positive laboratory and imaging findings. Patients also highlighted that test results impact their psychological well-being; despite burdensome symptoms and side-effects, positive results give patients hope and motivation to carry on: *"To get that M-component to fall or become invisible; these are such improvements that they do make even some more difficult side-effects acceptable."* The importance of a sustained positive treatment response (inclusive of reduction in symptoms) was also noted.

Unfavorable Effects: Side-Effects and Symptoms Negatively Impacting Patients' Life Expectancy and/or Quality of Life

Life-Threatening Side-Effects

Patients were afraid of serious side-effects that are life-threatening and could (permanently) damage other (vital) organs: *"Of course, any life-threatening side-effects (…) would make me think twice (…), as the side-effects would then be worse than the illness."* The following side-effects were raised: developing another cancer, stroke, heart failure, septic shock, and severe bleeding. Among these, the fear and uncertainty of developing another cancer was highlighted multiple times: *"You also have psychological consequences, the fear of a secondary cancer."*

Mobility Problems

Participants discussed which physical symptoms and side-effects significantly reduce their independence and *"control their life*." In particular, bone fractures were highlighted as major issues reducing patients' ability to move, and hence, reducing their independence and overall quality of life. Regarding bone fractures, several patients expressed the desire for an improvement in their "bone weakness" or a stabilization of their bone destruction. Aside from the negative *physical* impact of bone weakness, patients also described the negative *psychological* impact of these issues; the fear of being active due to a high risk of fractures: *"So it's the fear to try to do something and get a fracture, like that, break a bone, that fear."* Vice versa, patients argued that an increased ability to move would improve their psychological well-being. Some participants added that bone pain could be both due to the disease as well as due to treatment with bisphosphonates. The importance of the duration and

severity of their mobility problems was also stressed; while some patients expressed to be willing to accept temporary immobility, permanent immobility—requiring a rollator or wheelchair—was considered to be unacceptable by many. Patients also expressed the burden of the uncertainty of the duration of these problems: *"When will I be able to ski? Will I ever be able to ski? To do the things we did before."*

Symptoms associated with nerve damage and subsequent mobility problems were also discussed extensively. These issues commonly occur in extremities [feet, legs (calves), hand, fingers] and are particularly burdensome because they limit patient movement. Examples of these symptoms are: chronic (strange) sensations or tingling ("pins and needles"); over-sensitivity of the skin and bruises; numbness or reduced physical sensations (i.e., "sleeping" feet, fingers, and toes). Furthermore, participants described weakness or stiffness in feet and legs causing instability: *"Not having tingling in the feet. It makes walking difficult for me, the feeling of always having numb feet is very unpleasant."* Participants argued how improvements in these problems would be highly welcome: *"If something was found that would improve the whole tingling sensation that has become chronic."* Participants hoped these effects would improve once the treatment is stopped. Several feared constant mobility problems related to neuropathic symptoms and raised the uncertainty related to the duration of these issues. Those participants who themselves did not experience permanent side-effects, admitted to the psychological trauma of watching and knowing other MM patients who were permanently immobile and dependent on others.

Thinking Problems

Patients expressed fear of cognitive changes that would affect their daily mental activities such as: difficulties to think clearly, concentrate and pay attention (e.g., difficulties in reading a book, watching TV), memory loss, lower levels of consciousness, hallucinations (seeing, feeling, or sensing things that seem real but are not), dizziness, and confusion. Patients feared permanent and severe thinking problems that may reduce their independence, such as permanent memory loss (dementia) and definitive forgetfulness. Patients both speaking from experience, as well as those who had not yet experienced these symptoms, stated that such problems may prevent them from performing their professional and daily activities: *"Anything that could affect the brain or ability to concentrate (…) would really be a problem and would mean that I would have to give up my job which I really like and which forms a big part of my life."* Patients also felt that thinking problems may also result in a change to their identity, and negatively affect how they interact with others. Patients described how difficult it would be to have both thinking problems and mobility problems: *"So then there is not much left because you cannot read a book, (…) you cannot even do something else with your thoughts. And then in fact you can hardly do anything anymore." One* patient also described how a lack of ability to think—"*a complete loss of thinking*"—makes it difficult to plan anything in the future.

Infections

Patients discussed the negative consequences, both physically and mentally, of having an increased susceptibility to infections: *"so we are just afraid of infections, because our resistance is reduced"* (…) especially in view of the COVID-19 pandemic: *"Especially now in the corona crisis, it's not that I'm panicking, but I just keep my distance due to being afraid of infections because our resistance is so low."* Several specific infections and related problems were described such as lung infections, skin infections/disorders, throat infections, cold, flu, fever, and neutropenia.

Reduced Energy

Reduced energy and related problems, including extreme tiredness (also described as exhaustion, fatigue, complete lack of physical strength), sleeping problems, and breathlessness after minimal activity were discussed extensively. Patients described that these problems hinder them from performing daily activities, such as being physically active and independent and hence, significantly reduce their overall quality of life. Mirroring patients' reflections concerning the other side-effects, patients were afraid of permanent and severely reduced energy problems. Further, the psychological burden of having no physical strength and energy was highlighted: *"I'm always a very positive person, but then, my partner was even shocked, that my morale was below zero."* One patient even mentioned having experienced such severely reduced energy to the extent of losing the ability to see clearly.

Pain

Among the several types of pain that MM patients experienced, the most frequent and severe pains patients discussed were: bone pain in the back, chest, feet or hips, muscle pain and cramps, for example in the legs, and nerve pain (sharp, burning, or jabbing pain caused by nerve damage): *"I don't get up without back pain, after a walk I also have back pain."* The fear of constant and/or more severe pain was repeatedly mentioned, as well as the impact of pain on both the psychological and physical aspects of patients' life's: *"Due to bone pain, many activities are not possible"; "What you have to do to feel less pain is find a posture in which you don't feel it, because of course, it stops you from doing lots of things."*

Some patients described that there is currently no treatment (including morphine) that alleviates their pain. Similarly, patients hoped for a treatment that would alleviate or eliminate their pain, and thereby help them perform their daily activities and be independent: *"Above all, not feeling pain, when doing any daily activity."* A life without pain, was considered a (more) normal life: *"To be able to have a normal life, without pain."* One patient described the unbearable pain experienced due to shingles and post herpetic neuralgia. Some patients also described episodes of headache on the day of treatment, painful urination, and extreme stomach aches following stem cell transplantation: *"Severe stomach ache, I felt like I was on fire from the throat to the rectum."* One patient, however, mentioned to have never experienced any type of pain: *"I'm atypical, in the sense that I haven't felt any kind of pain."*

Emotional Problems

Patients raised the following emotional problems: (i) easily becoming emotional or becoming less emotional (apathetic); (ii) becoming more aggressive; (iii) feeling depressed; and (iv) feeling insecure because of changes to your body such as: weight loss,

weight gain, hair loss, dry eyes, stomach bloating, or abdominal distention—described by one patient as *"9 months pregnant"*—or loss of height due to compressed vertebrae. Patients were afraid of these problems as these often result in personality changes, are daily reminders of their cancer diagnosis and may also prevent patients from doing their daily activities. Several participants found changes to their body problematic as they had a negative impact on their emotional well-being: *"Because, you immediately look different, you don't feel good in your body."* One patient highlighted that these problems are often considered less important by "outsiders" in comparison to other, life-threatening effects: *"if you tell the doctors that too, and I understand that too, then it is seen as slightly less important."* It was not clear whether depression and becoming emotional were caused by treatment, the cancer directly, or because of knowing that their life might end soon. For emotional problems as well, the hope for non-lasting, temporary problems as opposed to permanent problems was expressed.

Eating and Digestive Problems

Nausea, vomiting, incontinence, constipation, diarrhea, loss of appetite, taste changes, and swallowing problems were all described as problems that significantly reduce patients' quality of life. As for other side-effects and symptoms, several patients were afraid that these problems would become permanent. One patient noted that these problems are problematic because they can lead to reduced social contacts. Whether or not patients had experienced these problems, as well as the severity of the problems they had experienced, depended on patients' particular treatment experience. For example, nausea, diarrhea (and consequently, reduced energy) was linked to treatment with lenalidomide. Some patients noted the burden of retracting gums and jaw problems that prevented them from eating properly and thought these problems were likely due to myeloma rather than treatments.

Vision Problems

Patients expressed the fear of suffering from (permanent) vision problems and becoming blind: *"I indeed know a number of people who (…) lost sight. That's a bit of my biggest fear."* One patient experienced transient vision changes: *"Certainly in the evening, when I am tired, I can hardly see."* Another patient noted that his vision problems could be due to treatment with lenalidomide. However, it remained largely unclear whether vision problems could be also side-effects of other treatments, due to the cancer itself or perhaps related to aging. For these problems as well, the hope for temporary side-effects as opposed to permanent changes was expressed.

Other Considerations Relevant for Myeloma Treatment

Preferences Differ According to Patients' Individual Characteristics and Experiences

Patients highlighted that their individual preferences were shaped by their previous treatment and disease experience. Particularly, whether they had experienced a certain symptom or side-effect, determined their views and preferences toward those symptoms and side-effects. Patients more frequently raised those symptoms and side-effects they had experienced, heard, or seen with other MM patients than those they or a close contact had never previously experienced: *"When one has gone through these (side-effects), one can think differently from one who hadn't experienced these."* Whereas, frequent symptoms and side-effects were discussed often, (e.g., bone fractures) others, more new or rare symptoms, were discussed by one or few patients (e.g., vision problems). Aside from treatment and disease experience, it also appeared that age, working status, whether patients have carers (such as children) may be important in determining and understanding why patients place more or less value on certain treatment characteristics. Further, participants who were professionally active frequently emphasized the impact of side-effects that limit their ability to continue working (such as cognitive problems).

The Burden of Uncertainty

On several occasions patients discussed the psychological burden of uncertainties including the cause, duration, type, and severity of side-effects and symptoms: *"What can be done about it, is it treatable or does it mean death? And will stopping (the treatment) help (…)? It's a terribly awkward thing."* Patients also expressed difficulty coping with the uncertainty of the duration of their side-effects and symptoms; patients were afraid that these side-effects would remain permanent or that the side-effects would permanently damage organs: "*So I am also a bit scared; are there no side-effects that are permanent, I am of course also a bit scared, but I still hope that that they really will disappear."* Regarding uncertainties related to the cause of their problems, patients discussed that at times they we unsure if their symptoms are related to treatment or their myeloma. Some participants stated the importance of managing expectations and that knowing what side-effects to expect before beginning treatment, is important to help them decide whether or not to start or continue a treatment: "*If it is known in advance, then it can be decided that I will not take this treatment because of it."* Participants also underlined the important role healthcare providers have in addressing these uncertainties: *"Doctors don't say much about these future side-effects (…) In fact, I've had to find out about things myself (…) Maybe [if I had this information] it would have made it easier to accept them and to live with them."*

Hope for New Treatments

Increasing life expectancy was also important to patients as some believed it would increase the chance that during the course of their disease a new, and ideally curative, MM treatment would become available. Patients seemed to be motivated by the knowledge that new treatments are currently being developed and that perhaps one of the novel therapies would become available for them, and in time.

Treatability of Side-Effects and Symptoms

Some patients highlighted that when side-effects and symptoms *"can be handled in some way,"* they become manageable and therefore less "important" than side-effects or symptoms for which no treatments are currently available. For example,

patients described that severe pains, the development of a new cancer, and cognitive changes are not treatable with current drugs, and therefore perceived as being worse: *"That is, severe pain and the onset of another cancer can really be quite difficult. These problems can be something that can't be helped at all."*

Risk Tolerance Differed Across Participants

Participants seemed to accept that treatments will always have side-effects: *"No matter what the treatment is, side-effects will appear. If I would fear the side-effects I would not be undergoing any treatment."* Naturally, they hoped for these side-effects to be as few and as mild as possible. However, the severity and number of risks patients were willing to accept in order to receive a certain benefit (i.e., their risk tolerance), differed across patients. Several patients noted that they were willing to accept even severe side-effects if that would be the condition to continue treatment. Others described only to be willing to accept severe side-effects on the condition that the treatment gives noticeable improvements in their disease.

Sharing Experiences Among Patients

Participants shared positive feedback regarding their participation in the discussion, they expressed a sense of comfort knowing that other patients experience similar issues. Some expressed that they were happy to be able to have participated in the discussion and share their experiences, feelings, and thoughts with other myeloma patients. The desire to continue the discussion after the focus group discussion was also expressed, as well as the suggestion of gathering via patient support groups.

DISCUSSION

This study identified treatment and disease-related characteristics (outcomes, side-effects and symptoms) and attribute levels that are key factors in determining treatment attitudes and choices by MM patients. In particular, MM patients across four European countries and with varying disease and treatment experience reached consensus on the importance of the following 11 themes of treatment outcomes, side-effects, and symptoms: life expectancy, life-threatening side-effects, treatment response, mobility problems, thinking problems, infections, reduced energy, pain, emotional problems, eating and digestive problems, and vision problems. Furthermore, this study highlights that MM patients are also concerned with the uncertainties regarding the durability of positive treatment outcomes, as well as the cause, severity and duration of their symptoms and side-effects. Regarding the attribute levels, MM patients feared only short-term positive treatment responses (benefits) but with permanent and severe side-effects and symptoms (risks) such as permanent severe pain or permanent blindness. Finally, this research presents and investigates a specific qualitative methodology in the context of patient preference studies, useful to further the methodological field and enable other researchers to investigate preferences and include results in decision-making that affects patients.

The attributes identified in this research will benefit stakeholders to identify priorities and unmet treatment needs for (new) treatments in MM. Specifically, results from this study point toward a need for MM treatment that not only focuses on extending patients' lives, but as well on improving those symptoms and side-effects that significantly impact MM patients' quality of life. Symptoms and side-effects explained and valued by patients are: mobility problems, thinking problems, increased susceptibility to infections, reduced energy, pain, emotional problems, eating and digestive problems, and vision problems. Furthermore, this research will inform what quality of life-related endpoints and outcomes are important to patients and should therefore be incorporated, in addition to traditional endpoints (such as progression-free survival and overall survival), in MM drug development and evaluation. Examples of HRQoL questionnaires commonly used in myeloma clinical trials are EORTC QLQ-MY2014, FACT-MM, EORTC-QLQ-C30, FACT/GOG-Ntx, and MDASI-MM. Among these, the FACT-MM, EORTC QLQ—MY20, and MDASI-MM are MM specific scales (i.e., including domains specifically related to MM) (50, 51). All of the items included in the MM specific scales were also identified in the current research, which is an important validation of our study results and vice versa, validates the work done to identify the items of these MM-specific scales. However, whereas these scales investigate patients' experience with these problems, the present study also reveals how important these problems are for patients, as well as why they are important and how they impact their lives. Further, this study reveals the following additional specific aspects of importance to MM patients, which are not included in all current MM-specific questionnaires: (i) fear of life-threatening effects, (ii) instability and strange sensations such as hypersensitivity of the skin, numbness or reduced physical sensations, (iii) weakness or stiffness of the legs, feet, toes, and extremities due to nerve damage, (iv) nerve pain, v) the following physical changes: weight loss, stomach bloating, loss of height due to compressed vertebrae, (vi) the following emotional changes: becoming apathetic, aggressive, depression, (vii) eating and digestive problems: such as nausea, vomiting, (viii) vision problems such as blurred vision, (vi) the psychological burden of coping with uncertainties about the durability of positive treatment response, the cause, duration, and severity of side-effects and symptoms.

Some of these additional findings may be explained by the fact that since the development of the HRQoL questionnaires, novel treatments with new side-effects and related uncertainties have been developed and administered to MM patients. For example, life-threatening neurotoxicity's and cytokine release syndrome are new side-effects associated with emerging treatments such as bispecific T-cell engagers and CAR-T therapies, which are not captured by previous questionnaires but in this study were captured in the context of life-threatening side-effects or side-effects that are so significant that they require hospitalization for monitoring (37). Further, (recently) approved drug therapies for MM have been associated with visual changes such as blurred vision and decrease visual acuity (52). The identification of these additional items provides a rationale

for including these aspects in a next revision of the HRQoL questionnaires. Systematically including the items identified in this type of research in clinical development, regulatory benefit-risk assessment, HTA/reimbursement decisions and post-marketing decisions, could result in a more patient-centric drug development and evaluation process. Conversely, when there is no evidence that a MM drug targets any of the attributes identified in this study, it may be recommended that such evidence needs to be collected before or after marketing authorization and/or reimbursement and should subsequently be taken into account when designing clinical or real-world evidence research protocols.

This research revealed areas of importance where clear information about MM treatments is needed to inform drug development, regulators, HTA bodies, and healthcare providers. When there is a lack of knowledge and information, e.g., regarding the long-term effects and their severity, this uncertainty should be made public, in an accessibly way to patients. This starts from the clinical trial evidence reported by the pharmaceutical company toward regulators (in clinical trial databases, the marketing application and then reported on the European Public Assessment Report (EPAR), Summary of Product Characteristics (SmPC) and EMA website), and downstream when reporting the clinical trial evidence toward HTA agencies, healthcare providers and patients. MM healthcare professionals, patients, regulators and HTA bodies/payers should be able to easily retrieve this information in clinical trial databases, marketing materials and package inserts of MM drugs. Accurate and clear information about these aspects and uncertainties would result in more informed decision-making by regulators, HTA bodies, physicians and patients. Particularly in the clinical, individual treatment decision-making between healthcare providers and patients, transparent communication before and during treatment may increase patients' satisfaction with the treatment decision and motivation to start or continue a certain treatment and therefore result in better outcomes and patient quality of life as expectations are managed.

Finally, this study may inform the development of PREFER recommendations and future guidance regarding patient preference studies (and methodology) in the context of drug development and evaluation. More specifically, this study derives 10 experience-based learnings regarding the design, conduct and analysis of qualitative research aiming to develop attributes and levels for inclusion in subsequent preference surveys, useful for the PREFER recommendations and future guidance regarding patient preference studies (**Table 2**).

If preference studies are to inform drug development, regulatory, and reimbursement decisions, it is essential to reflect on how the key attributes and levels for inclusion in preference survey were identified. Misspecification of attributes may lead to biased findings, and hence, biased preference studies, hence undermining development, regulatory, and reimbursement decisions. It is therefore important to reflect on how the characteristics identified in this study compare to those identified in previous preference studies among MM patients. Comparing the attributes found in this study to those identified in the scoping review of previous preference studies (**Appendix 2**), reveals that a large portion of these studies used attributes that were not appointed by patients themselves but developed using top-down methods, starting from the perspective of researchers, developers or decision-makers. Previous preference studies have also used attributes that were associated with one specific therapy. In contrast, this study identified patient-relevant attributes across different therapies (for example, novel immunotherapies), countries and directly from myeloma patients. There are several potential reasons for differences in attributes identified across preference studies. Attribute identification, to date, is mostly done through studies involving literature reviews and qualitative empirical studies. Qualitative empirical research always requires contextualizing the results in view of the research setting. This implies that several factors may differ across qualitative studies, such as the selected sample, the stakeholder conducting study (e.g., a patient organization vs. a pharmaceutical company), the researcher or decision-makers' interests, the time of study and the specific questions asked. All of these factors need to be taken into account when looking at the results (i.e., the identified attributes) as a difference in any of these may already explain a difference in the identified attributes. Differences in methodology for attribute and level identification are likely triggered by uncertainties regarding the best methodological approach for this study type. While the present study derived experience-based learnings, the methodological field is continuously and rapidly evolving, and other qualitative study methods are also under investigation. Combining and comparing experiences and methodological understanding from different qualitative approaches will be useful to inform the development of a standardized approach for use by all stakeholders across disease areas. Furthermore, methodological understanding will assist with the development of a validated framework for designing and conducting preference studies aiming to inform drug development and evaluation.

Although the attributes reflect areas of consensus, there was heterogeneity with regards to the value each patient attached to the attributes. In particular, participants more frequently valued those symptoms and side-effects they had previously experienced. Further, participants who were older, had undergone more treatments, or had no young children seemed to attach more importance to quality of life related attributes (such as pain) than life expectancy, and vice versa. Participants who were professionally active frequently emphasized the impact of (cognitive) side-effects on their ability to continue working. Likewise, participants' willingness to accept more reduction in quality of life (i.e., symptoms and risk of life-threatening side-effects) in return for a potential increase in life expectancy differed across participants, depending on their individual situation and personal attitudes. These findings underscore the importance of further quantitative preference research that statistically substantiates these hypotheses and provides a quantified understanding of individual patients' values of life extension vs. symptom reduction vs. risk of life-threatening side-effects.

The existence of patient subgroups with systematically different preferences may be viewed both as a challenge and opportunity from the perspective of decision-makers (industry,

TABLE 2 | Experience-based learnings regarding the design, conduct, and analysis of qualitative research for informing subsequent quantitative preference surveys in the context of drug development and evaluation −10 avenues for optimization.

Experience-based learnings regarding qualitative research for informing subsequent quantitative preference surveys
1. **Since patients are disease-experts, experiencing the benefits and risks of treatment on a daily basis, they should be systematically and continuously involved, both as study participants and as study partners.** - The involvement of patients and patient organizations is essential to ensure that the attributes and levels are relevant, comprehensive, and understandable to patients participating in the subsequent quantitative survey. - Their involvement throughout the analysis and attribute selection process guarantees that patients' points of view are reflected in an accurate, unbiased, and understandable way, and thereby improve the survey validity. - In return, patients may benefit from learning about treatments obtained through their involvement. Patient organizations may benefit from using this methodology as an evidence-based way to generate data and best represent the patients' voice. - The results of preference studies may provide patient organizations an evidence-based perspective when communicating with regulatory and reimbursement bodies regarding the priorities and needs of patient communities.
2. **Before undertaking a preference study, researchers should investigate the availability and usefulness of previous preference studies (qualitative or quantitative) for informing the attributes and levels for inclusion in their preference survey.** - If previous studies are available in the disease or treatment context of interest, researchers should assess to what extent the attributes and levels of those studies are transferable and applicable to their research context and aims. This will help determine the necessity of conducting a "new" qualitative study. - In this study, the goal was to identify attributes and levels relevant to patients with varying treatment exposure, disease history, age, or country of origin. This contrasted with previously conducted preference studies identified in our scoping review, which only included patients with a specific disease and treatment experience (e.g., only the relapsed refractory patient population) or used attributes related to a specific treatment. Therefore, a new study considering the recruitment of patients heterogeneous in terms of treatment experience and disease stage was necessary. - Preference researchers aiming to identify attributes and levels relevant to patients with various treatment exposures, disease history, age and country of origin should consider conducting a new qualitative study if a similar qualitative study aiming to pursue this objective is unavailable. - Furthermore, experience from this study highlights that it is desirable: (i) to include a heterogeneous, inclusive sample of patients in terms of treatment exposure and disease history as these variables affected patients' rankings and views, (ii) to include patients from different countries to help ensure a diverse sample of patients is included. - Even if a previous preference study with similar aims is available, preference researchers should assess whether the findings of the study are up-to-date, appropriately designed and comprehensive (i.e., whether they consider novel treatments, as well as related side-effects, outcomes and uncertainties).
3. **Researchers should ensure the study is designed to meet the specific needs of the study participants.** - Key decision points which should be tailored toward the particular patient population of interest are the selection of the qualitative data collection method (the feasibility and usefulness of (telephone) interviews vs. (online) focus group discussions; time, feasibility of ranking exercise) and the development of the questions (via review and pilot testing to ensure relevance, understandability and accuracy). - Input from patients, patient organizations, and/or healthcare providers should help ensure the study is designed in such a way that is easiest for the particular patient population. - In this study, patients, patient organizations, and healthcare providers confirmed that both individual interviews and focus group discussions would be possible and agreed that group interaction would be useful between patients and nominal group technique to trigger discussion around the most important treatment characteristics. In this study, face-to-face discussions were initially planned as myeloma patients are elderly and more likely gravitate away from technology. - However, future researchers may need to balance the utility of increased interaction via focus group discussions vs. the more practical feasibility of individual interviews in view of the targeted participant population. For example, interviews allow for more flexibility in choosing various dates for participation and discussions can take place via telephone and not necessarily online, which is especially relevant in view of COVID19 (and potentially beneficial for elderly patients or those who are not well-versed in technology).
4. **Qualitative studies may also be used to explore which patient variables (such as treatment exposure, disease history, age, or country of origin) should be useful to inform the quantitative survey.** - In this study, patients highlighted that treatment and disease experience strongly influenced their views. - Hence, these variables should be collected and used in qualitative and quantitative preference studies to contextualize both the qualitative and quantitative preference study results.
5. **Obtaining input from stakeholders with expertise in the relevant disease and treatment context (patients, patient organizations, healthcare practioners) and stakeholders with methodological expertise—should help inform the development of attributes and levels.** - Patients can critically reflect on the attributes and levels and thereby avoid inadvertent omittance of attributes and levels of potential importance, as this may bias findings. - Clinicians help ensure the attributes and levels are clinically plausible. - Input from preference research experts helps ensuring the rules of attribute and level development are adhered to.
6. **In view of the multitude of methodological choices in attribute and level development, transparently documenting and describing the study design and methodological choices as well as its limitations and challenges is essential for enabling reviewers to contextualize the study results and evaluate their usefulness for decision-making.**
7. **Before starting a preference study, research teams should investigate the necessity of obtaining ethical approval and contractual agreements with hospitals in all countries where data collection is planned and/or hospitals are involved in data collection, respectively.** - Because ethical approval for this type of research is regulated nationally, researchers should investigate for each country separately, whether the study requires obtaining ethical approval, and if so, consider the time and administrative burden associated with filing and obtaining ethical approval. - Experience from this study reveals that the necessity of obtaining ethical approval depends on whether the study is considered in scope of the national law regulating this type of research. In this study, ethical approval was applied for and obtained in all countries where patients were included. However, during the submission and approval process, it appeared that the study did not fall in the scope of the national law requiring ethical approval in Belgium and Finland, where the process of obtaining ethical approval took particularly long. Conversely, the procedure took less time in Spain and Romania, where the ethical committee did not explicitly mention whether the study required their approval.

(Continued)

TABLE 2 | Continued

8. **Research teams should consider the input, time and administrative burden for involved clinical partners associated with these steps and ensure flexibility in terms of timelines, if ethical approval, hospital contracts, and patient recruitment relies on their cooperation.**
9. **Before starting the study, researchers should investigate how patient recruitment and data collection will take place in practice.** In this study, the involvement of oncology nurses and clinicians proved to be crucial for implementing the recruitment and practical organization of the discussions.
10. **Preference researchers should consider the practical and methodological implications of COVID19 and/or potential subsequent pandemics and how their study designs could best meet patient needs.**
    - In this study, this was especially relevant as myeloma patients have increased susceptibility to infections.
    - COVID19 substantially delayed the study, e.g., due to required changes to the initial research protocol to adhere to hospital requirements in view of patient contact restrictions, and increased workloads for cooperating healthcare professionals, ethical committees and hospital administration offices.
    - Future qualitative preference research may likely require digital and online formats for data collection, as well as phone calls, virtual encounters, instead of face-to-face contacts.

drug developers, and HTA bodies) who develop, authorize and reimburse drugs for groups of patients and not for individual patients. In particular, it raises the question whether their decisions need to be tailored toward specific patient populations whose preferences align with the product characteristics being developed or evaluated. The existence of subgroups in the MM patient population with systematically different relative attribute values and risk tolerances may also inform the identification of key areas of unmet needs, benefits and risks for this relevant population. For example, a company could submit clinical evidence to apply for marketing authorization and reimbursement for the elderly, more treatment experienced MM population (also called the relapsed refractory RRMM) and clinical trial results may indicate that the treatment causes quality of life related problems (such as mobility, vision problems) in this population. If results from a preference study reveal that this population finds quality of life related attributes (such as mobility, vision problems) more important than life expectancy, then decision-makers should likely place more value on these risks during their assessment of treatment outcomes and ensure these risks are taken into account during their decision-making.

As for the limitations, it is important to reflect on the impact of the COVID-19 on this research. This is especially relevant since this study consisted of qualitative discussions with MM patients, who have a higher susceptibility to infections. Conducting this study during COVID-19 required flexibility from both participants and the study team. For the online and telephone discussions, it is likely that participants, who were not comfortable with online discussions or telephone (e.g., older participants), were less likely to participate. The study team tried to be as inclusive as possible during recruitment, by offering both face-to-face and online discussions, according to the preferences of the participants and the local social distancing and hospital guidelines. Further, technical support for participants was given throughout the entire study. A steps-wise guideline explaining the practicalities of the discussion beforehand, and ensuring there was an opportunity, before the session, for participants to test whether they could participate in the discussion. Still, the median age of diagnosis of patients included in this study was 55, which is 11 years younger than the median age reported by Kazandijan in 2016 and 14 years younger than the average age of diagnosis reported by ASCO in 2020 (53, 54). However, there was a large age range between the youngest and oldest patient (46–73), and therefore the attributes captured in this study for inclusion in the next quantitative phase also reflect those that are most important for elderly patients. Further regarding generalizability, it is important to note that the purpose of this study was not to make statements about a population larger than the included sample. Rather, it aimed to gain in-depth insight into the opinions of patients participating in the discussions including which attributes are important to them and why.

Participant heterogeneity in terms of treatment and disease experience [including the type of treatments received, disease stage (i.e., refractory level and number of previous treatments, experienced side-effects)] and demographic characteristics were introduced to avoid distortions in the data; it was envisioned that these personal characteristics and experiences could influence participants' opinions. Hence, heterogeneity among the focus group participants, particularly regarding their disease and treatment experience, triggered interactions between patients with varying backgrounds and facilitated discussions around a large range of symptoms, treatment outcomes, and side-effects, even though some individual participants (earlier diagnosed, with less treatment experience) had not experienced them themselves. The inclusion of a heterogeneous group of participants and their interactions, due to the focus group methodology, helped ensure that the identified attributes and levels are not geared to only patients with a particular background (e.g., with a particular therapy experience, disease experience, level of education). Likewise, to ensure that patients would be able to discuss "future" treatment outcomes and side-effects of novel treatments or treatments under development (i.e., symptoms they had not yet experienced themselves, such as those associated with bispecific T-cell engagers and CAR-T), the focus group discussions included endpoints and adverse events reported in phase 3 MM clinical trials from 2010 onwards (found in the literature review). Further, the attribute selection also captured the favorable and unfavorable effects of (recently) approved MM drug therapies.

The results of this (and other qualitative research) are time, study context and participant bound and hence need to be interpreted considering the specific time period and (drug therapy) context the study took place as well as in view of the type of participants that took part. For example, this study took place during COVID19 and this may have led to the fact that patients more frequently raised their increased susceptibility to infections. Further, the results should be viewed in the specific drug therapy context patients are

experiencing currently; the MM treatment context is rapidly evolving and a significant number of new and emerging treatments have been introduced. These novel treatments are bringing prolonged survival but also potential side-effects of uncertain severities and duration on the long term. For example, new treatments such as novel immunotherapies (e.g., bispecific T-cell engagers and CAR-T) have been associated with (acute) side-effects and these may cause psychological and physical distress to patients. The introduction of these new therapies and rapidly evolving drug therapy context likely explains why patients expressed the psychological burden of their uncertainties related to their side-effects and efficacy outcomes, particularly regarding treatments only being marketed and prescribed for a relatively short time period. This study highlights that patients are concerned with uncertainties regarding the long-term duration and severity of their side-effects (such as neuropathic, mobility and vision problems) and about how long the treatment will continue to work for them. Information about which uncertainties are most important to patients may help stakeholders (drug developers, regulators, HTA bodies, physicians) by providing insights about the uncertainties most pressing to patients; to be considered during decisions about evidence generation, marketing authorization, market access and subsequently managed in the individual treatment decision-making context.

Several patient characteristics (disease stage such as refractory level and number of previous treatments), symptom experience, and demographic data (including country of origin, health literacy/education) likely influence preferences, i.e., the value that participant place on attributes (outcomes, symptoms, and side-effects). For example, MM patients that are younger, less frail and who have limited treatment exposure may tolerate and perceive side effects differently. Therefore, it will be important to investigate, transparently describe, and consider the impact of these patient variables on preferences, and to describe this impact as well as their influence on preferences. Therefore, in the survey following this qualitative study, we aim to characterize and describe the demographics of the study population using patient characteristics when reporting the results. Additionally, in the follow up quantitative survey, research will focus on the statistically significant impacts of patient characteristics on preferences.

CONCLUSION

This study gained an in-depth understanding of the treatment and disease-related characteristics (outcomes, side-effects, and symptoms) and types of attribute levels (severity, duration) that are most important to MM patients. Results point toward a need for MM drug development, evaluation, and individual treatment decision-making that not only focuses on extending patients' lives, but that addresses symptoms and side-effects that significantly impact MM patients' quality of life. This study underlines the need for communication toward patients about the short and long-term effects of MM treatments. Finally, this study may help stakeholders to understand which quality of life-related treatment outcomes are most important to MM patients and therefore should be considered for systematic incorporation in MM drug development, evaluation and clinical practice.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they contain information that could compromise participants' privacy and consent. Requests to access the datasets should be directed to rosanne.janssens@kuleuven.be.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee UZ/KU Leuven (reference S63620), the Clinical Institute Fundeni (reference 20637), the Research Ethics Committee of the Bellvitge University Hospital reference PR117/20 (CSI 20/26), and the Helsinki University Hospital (reference 1413/2020). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RJ drafted the manuscript. All authors provided substantial input in the study design, critical revision of the manuscript, and read and approved the final manuscript.

FUNDING

This study is part of the PREFER project. The *Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle* (PREFER) project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement N. 115966. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

ACKNOWLEDGMENTS

The authors are extremely grateful to the patients participating in the discussions, for sharing their experiences and valuable contributions. A special thank you to Dr. Margaux Verschueren, clinical psychologist and researcher (KU Leuven, School Psychology and Development in Context) for sharing her methodological expertise regarding statistical methods and for helping with the statistical analysis.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.686165/full#supplementary-material

REFERENCES

1. van Overbeeke E, Janssens R, Whichello C, Schölin Bywall K, Sharpe J, Nikolenko N, et al. Design, conduct, and use of patient preference studies in the medical product life cycle: a multi-method study. *Front Pharmacol.* (2019) 10:1395. doi: 10.3389/fphar.2019.01395
2. Craig BM, Lancsar E, Mühlbacher AC, Brown DS, Ostermann J. Health preference research: an overview. *Patient.* (2017) 10:507–10. doi: 10.1007/s40271-017-0253-9
3. US Food and Drug Administration. *Patient Preference Information (PPI) in Medical Device Decision-Making.* (2020). Available online at: https://www.fda.gov/about-fda/cdrh-patient-engagement/patient-preference-information-ppi-medical-device-decision-making (accessed May 17, 2021).
4. European Medicines Agency. *EMA Regulatory Science to 2025. - Strategic reflection.* (2020). Available online at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf (accessed May 17, 2021).
5. Hines PA, Janssens R, Gonzalez-Quevedo R, Lambert A, Humphreys AJ. A future for regulatory science in the European Union: the European Medicines Agency's strategy. *Nat Rev Drug Discov.* (2020) 19:293–4. doi: 10.1038/d41573-020-00032-0
6. Hines PA, Gonzalez-Quevedo R, Lambert A, Janssens R, Freischem B, Torren Edo J, et al. Regulatory science to 2025: an analysis of stakeholder responses to the European Medicines Agency's strategy. *Front Med.* (2020) 7:508. doi: 10.3389/fmed.2020.00508
7. Janssens R, Russo S, van Overbeeke E, Whichello C, Harding S, Kubler J, et al. Patient preferences in the medical product life cycle: what do stakeholders think? Semi-structured qualitative interviews in Europe and the USA. *Patient.* (2019) 12:513–26. doi: 10.1007/s40271-019-00367-w
8. Janssens R, van Overbeeke E, Verswijvel L, Meeusen L, Coenegrachts C, Pauwels K, et al. Patient involvement in the lifecycle of medicines according to belgian stakeholders: the gap between theory and practice. *Front Med.* (2018) 5:285. doi: 10.3389/fmed.2018.00285
9. van Overbeeke E, Whichello C, Janssens R, Veldwijk J, Cleemput I, Simoens S, et al. Factors and situations influencing the value of patient preference studies along the medical product lifecycle: a literature review. *Drug Discov Today.* (2019) 24:57–68. doi: 10.1016/j.drudis.2018.09.015
10. Whichello C, van Overbeeke E, Janssens R, Schölin Bywall K, Russo S, Veldwijk J, et al. Factors and situations affecting the value of patient preference studies: semi-structured interviews in Europe and the US. *Front Pharmacol.* (2019) 10:1009. doi: 10.3389/fphar.2019.01009
11. Muhlbacher AC, Kaczynski A. Making good decisions in healthcare with multi-criteria decision analysis: the use, current research and future development of MCDA. *Appl Health Econ Health Policy.* (2016) 14:29–40. doi: 10.1007/s40258-015-0203-4
12. Postmus D, Mavris M, Hillege HL, Salmonson T, Ryll B, Plate A, et al. Incorporating patient preferences into drug development and regulatory decision making: results from a quantitative pilot study with cancer patients, carers, and regulators. *Clin Pharmacol Therap.* (2016) 99:548–54. doi: 10.1002/cpt.332
13. Postmus D, Richard S, Bere N, van Valkenhoef G, Galinsky J, Low E, et al. Individual trade-offs between possible benefits and risks of cancer treatments: results from a stated preference study with patients with multiple myeloma. *Oncologist.* (2018) 23:44–51. doi: 10.1634/theoncologist.2017-0257
14. Tervonen T, Gelhorn H, Sri Bhashyam S, Poon JL, Gries KS, Rentz A, et al. MCDA swing weighting and discrete choice experiments for elicitation of patient benefit-risk preferences: a critical assessment. *Pharmacoepidemiol Drug Safety.* (2017) 26:1483–91. doi: 10.1002/pds.4255
15. Tervonen T, Pignatti F, Postmus D. From individual to population preferences: comparison of discrete choice and dirichlet models for treatment benefit-risk tradeoffs. *Med Decision Making.* (2019) 39:879–85. doi: 10.1177/0272989X19873630
16. Llewellyn-Thomas HA, Crump RT. Decision support for patients: values clarification and preference elicitation. *Med Care Res Rev.* (2013) 70(1 Suppl):50s−79s. doi: 10.1177/1077558712461182
17. Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev.* (2017) 4:Cd001431. doi: 10.1002/14651858.CD001431.pub5
18. Stiggelbout AM, Pieterse AH, De Haes JC. Shared decision making: concepts, evidence, and practice. *Patient Educ Couns.* (2015) 98:1172–9. doi: 10.1016/j.pec.2015.06.022
19. Advancing Regulatory Science. *Advancing Use of Patient Preference Information as Scientific Evidence in Medical Product Evaluation [WebContent]. Office of the Commissioner.* (2018). Available online at: https://www.fda.gov/scienceresearch/specialtopics/regulatoryscience/ucm574320.htm (accessed May 17, 2021).
20. Patient Preference Information. *Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, De Novo Requests, Inclusion in Decision Summaries Device Labeling: Guidance for Industry, Food Drug Administration Staff and Other Stakeholders.* Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health and Center for Biologics Evaluation and Research (2016).
21. U.S. Food and Drug Administration. *Patient-Focused Drug Development: Collecting Comprehensive Representative Input - Guidance for Industry, Food Drug Administration Staff, Other Stakeholders - GUIDANCE.* Silver Spring, MD: U.S. Department of Health and Human Services Food and Drug Administration CfDEaRC, Center for Biologics Evaluation and Research (CBER) (2018).
22. European Medicines Agency. *The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Reflection Paper on Proposed ICH Guideline Work to Advance Patient Focused Drug Development,* (Amsterdam) (2020). p. 5.
23. Bouvy JC, Cowie L, Lovett R, Morrison D, Livingstone H, Crabb N. Use of patient preference studies in HTA decision making: a NICE perspective. *Patient.* (2020) 13:145–9. doi: 10.1007/s40271-019-00408-4
24. Bouvy J. *Patient Preferences Studies: How NICE Aims to Make Use of Them.* (2019). Available online at: https://www.nice.org.uk/news/blog/patient-preferences-studies-how-nice-could-make-use-of-them#:~:text=Patient%20preferences%20is%20the%20term,methods%20of%20surveying%20patient%20preferences (accessed May 17, 2021).
25. Cook NS, Cave J, Holtorf A-P. Patient preference studies during early drug development: aligning stakeholders to ensure development plans meet patient needs. *Front Med.* (2019) 6:82. doi: 10.3389/fmed.2019.00082
26. Janssens R, Huys I, van Overbeeke E, Whichello C, Harding S, Kübler J, et al. Opportunities and challenges for the inclusion of patient preferences in the medical product life cycle: a systematic review (accepted 23/07/2019). *BMC Med Inform Decis Mak.* (2019) 19:189. doi: 10.1186/s12911-019-0875-z
27. Chachoua L, Dabbous M, François C, Dussart C, Aballéa S, Toumi M. Use of patient preference information in benefit–risk assessment, health technology assessment, and pricing and reimbursement decisions: a systematic literature review of attempts and initiatives. *Front Med.* (2020) 7:543046. doi: 10.3389/fmed.2020.543046
28. *preferences P-p*. Available online at: https://www.imi-prefer.eu/ (accessed May 17, 2021).
29. de Bekker-Grob EW, Berlin C, Levitan B, Raza K, Christoforidi K, Cleemput I, et al. Giving patients' preferences a voice in medical treatment life cycle: the PREFER public-private project. *Patient.* (2017) 10:263–6. doi: 10.1007/s40271-017-0222-3
30. Brod M, Tesler LE, Christensen TL. Qualitative research and content validity: developing best practices based on science and experience. *Qual Life Res.* (2009) 18:1263–78. doi: 10.1007/s11136-009-9540-9
31. Durosini I, Janssens R, Arnou R, Veldwijk J, Smith MY, Monzani D, et al. patient preferences for lung cancer treatment: a qualitative study protocol among advanced lung cancer patients. *Front Public Health.* (2021) 9:622154. doi: 10.3389/fpubh.2021.622154
32. Kerr C, Nixon A, Wild D. Assessing and demonstrating data saturation in qualitative inquiry supporting patient-reported outcomes research. *Expert Rev Pharmacoecon Outcomes Res.* (2010) 10:269–81. doi: 10.1586/erp.10.30
33. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* (2017) 28(suppl_4):iv52–61. doi: 10.1093/annonc/mdx096

34. Raab MS, Cavo M, Delforge M, Driessen C, Fink L, Flinois A, et al. Multiple myeloma: practice patterns across Europe. *Br J Haematol.* (2016) 175:66–76. doi: 10.1111/bjh.14193
35. Röllig C, Knop S, Bornhäuser M. Multiple myeloma. *Lancet.* (2015) 385:2197–208. doi: 10.1016/S0140-6736(14)60493-1
36. Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Castillo J, et al. NCCN guidelines insights: multiple myeloma, Version 3.2018. *J Natl Compre Cancer Network.* (2018) 16:11–20. doi: 10.6004/jnccn.2018.0002
37. Slaney CY, Wang P, Darcy PK, Kershaw MH. CARs versus BiTEs: a Comparison between T cell-redirection strategies for cancer treatment. *Cancer Discov.* (2018) 8:924–34. doi: 10.1158/2159-8290.CD-18-0297
38. European Commission. *Patient Preferences in Benefit Risk Assessments During the Drug Life Cycle*. Available online at: https://cordis.europa.eu/project/id/115966 (accessed May 17, 2021).
39. Coast J, Al-Janabi H, Sutton EJ, Horrocks SA, Vosper AJ, Swancutt DR, et al. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. *Health Econ.* (2012) 21:730–41. doi: 10.1002/hec.1739
40. Hollin IL, Craig BM, Coast J, Beusterien K, Vass C, DiSantostefano R, et al. Reporting formative qualitative research to support the development of quantitative preference study protocols and corresponding survey instruments: guidelines for authors and reviewers. *Patient.* (2020) 13:121–36. doi: 10.1007/s40271-019-00401-x
41. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, et al. Conjoint analysis applications in health–a checklist: a report of the ISPOR good research practices for conjoint analysis task force. *Value Health.* (2011) 14:403–13. doi: 10.1016/j.jval.2010.11.013
42. Hensher DA, Rose JM, Greene WH. *Applied Choice Analysis*. 2 ed. Cambridge: Cambridge University Press (2015). doi: 10.1017/CBO9781316136232
43. Lacey A, Luff D. Qualitative *Research Analysis.* Yorkshire: The NIHR RDS for the East Midlands (2007).
44. Hiligsmann M, van Durme C, Geusens P, Dellaert BG, Dirksen CD, van der Weijden T, et al. Nominal group technique to select attributes for discrete choice experiments: an example for drug treatment choice in osteoporosis. *Patient Prefer Adherence.* (2013) 7:133–9. doi: 10.2147/PPA.S38408
45. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *Int J Clin Pharm.* (2016) 38:655–62. doi: 10.1007/s11096-016-0257-x
46. Morgan DL. Focus groups. *Ann Rev Sociol.* (1996) 22:129–52. doi: 10.1146/annurev.soc.22.1.129
47. Guest G, Bunce A, Johnson L. How many interviews are enough?:An experiment with data saturation and variability. *Field Methods.* (2006) 18:59–82. doi: 10.1177/1525822X05279903
48. Hennink MM, Kaiser BN, Weber MB. What influences saturation? Estimating sample sizes in focus group research. *Qual Health Res.* (2019) 29:1483–96. doi: 10.1177/1049732318821692
49. Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Fam Med.* (2004) 36:588–94.
50. FACT-MM. *Functional Assessment of Cancer Therapy - Multiple Myeloma.* Available online at: https://www.facit.org/measures/FACT-MM (accessed May 17, 2021).
51. EORTC QLQ – MY20 Available online at: https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-MY20-English.pdf (accessed May 17, 2021).
52. Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol.* (2020) 21:207–21. doi: 10.1016/S1470-2045(19)30788-0
53. Kazandjian D. Multiple myeloma epidemiology and survival: a unique malignancy. *Semin Oncol.* (2016) 43:676–81. doi: 10.1053/j.seminoncol.2016.11.004
54. ASCO. Available online at: https://www.cancer.net/cancer-types/multiple-myeloma/risk-factors#:~:text=Myeloma%20occurs%20most%20commonly%20inoccur%20in%20people%20under%2040 (accessed May 17, 2021).

Disclaimer: This article and its contents reflect the view of the authors and not the view of PREFER, IMI, the European Union or EFPIA.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

PERSPECTIVE
published: 27 October 2021
doi: 10.3389/fmed.2021.730021

A Learning Health System Framework to Operationalize Health Data to Improve Quality Care: An Australian Perspective

Joanne C. Enticott[1,2,3]*, *Angela Melder*[2,3], *Alison Johnson*[3], *Angela Jones*[3], *Tim Shaw*[4,5], *Wendy Keech*[6], *Jim Buttery*[7] *and Helena Teede*[2,3]*

[1] Southern Synergy, Department of Psychiatry, Monash University, Melbourne, VIC, Australia, [2] Monash Centre for Health Research and Implementation, Monash University, Clayton, VIC, Australia, [3] Monash Partners Academic Health Science Centre, Clayton, VIC, Australia, [4] Sydney Health Partners, Sydney, NSW, Australia, [5] Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia, [6] Health Translation South Australia, Adelaide, SA, Australia, [7] Centre for Health Analytics, Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia

OPEN ACCESS

Edited by:
Tania Bubela,
Simon Fraser University, Canada

Reviewed by:
Carla Matos Torre,
University of Lisbon, Portugal
Frits Lekkerkerker,
Consultant, Amsterdam, Netherlands

***Correspondence:**
Joanne C. Enticott
joanne.enticott@monash.edu
Helena Teede
helena.teede@monash.edu

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: 28 June 2021
Accepted: 16 September 2021
Published: 27 October 2021

Citation:
Enticott JC, Melder A, Johnson A, Jones A, Shaw T, Keech W, Buttery J and Teede H (2021) A Learning Health System Framework to Operationalize Health Data to Improve Quality Care: An Australian Perspective. Front. Med. 8:730021. doi: 10.3389/fmed.2021.730021

Our healthcare system faces a burgeoning aging population, rising complexity, and escalating costs. Around 10% of healthcare is harmful, and evidence is slow to implement. Innovation to deliver quality and sustainable health systems is vital, and the methods are challenging. The aim of this study is to describe the process and present a perspective on a coproduced Learning Health System framework. The development of the Framework was led by publicly funded, collaborative, Academic Health Research Translation Centres, with a mandate to integrate research into healthcare to deliver impact. The focus of the framework is "learning together for better health," with coproduction involving leadership by an expert panel, a systematic review, qualitative research, a stakeholder workshop, and iterative online feedback. The coproduced framework incorporates evidence from stakeholders, from research, from data (practice to data and data to new knowledge), and from implementation, to take new knowledge to practice. This continuous learning approach aims to deliver evidence-based healthcare improvement and is currently being implemented and evaluated.

Keywords: data-driven learning, learning health care system, healthcare improvement, quality, translational

INTRODUCTION

Data and benchmarking alone do not drive healthcare improvement, and core challenges remain, with estimates of around 30% of care is low value and 10% potentially harmful (1). Furthermore, effective sustainable healthcare improvement appears to be an intractable problem. There is a recognized vital need for systems-level change to improve healthcare using an iterative learning health system (LHS) approach (1, 2). The LHS broadly encompasses the operationalization and conversion of routinely collected health data into useful information to enable informed, timely decisions to improve quality healthcare and health outcomes (2–8). Herein, we describe the coproduction process and the outcome for the development of the Monash Partners LHS framework, integrating research and data utilization into healthcare to improve outcomes.

This framework development occurred in the context of publically funded Academic Health Science Centres (AHSC) in Australia, where AHSCs have a strong focus on research translation (9, 10) and are tasked with driving "Better Health through Research." Monash Partners Academic Health Science Centre (Monash Partners) is a partnership between leading health services, teaching, and research organizations, accredited by the Australian National Health and Medical Research Council (NHMRC). The mission of Monash Partners is to connect researchers, clinicians, and the community to innovate for better health and deliver health impact. Monash Partners led this work engaging all 10 NHMRC accredited Australian Research Translation Centres, under the auspices of the Australian Health Research Alliance (AHRA: www.ahra.org.au). AHRA has a national reach across 95% of academic and research teams of Australia, and over 80% of acute health services are collaborating to improve health nationally (9). AHRA formed a data-driven healthcare improvement national system level initiative to "improve health outcomes across our community, through data-driven innovation and care." In this context, Monash Partners led a rigorous national priority setting process across AHRA centres, communities, healthcare, government, and other stakeholders. The top priority was to create data-driven hubs for healthcare improvement or LHS, across the AHRA centres.

With ever increasing data availability, there is a growing interest in how best to use it to inform decision making in healthcare delivery (2). Systems are needed to ensure the most relevant information, and evidence can guide healthcare decision making (11, 12). Improved healthcare requires systems in which routine data, from service delivery, and patient care, can lead to iterative cycles of knowledge generation and improvement in healthcare, as a result of daily practice (5, 6). Informed decision making is needed at all levels of healthcare, including decisions made by policymakers, hospital executives, clinicians, and by patients themselves (13). In this perspective article, we outline the codevelopment process, present the codesigned framework, and describe the ongoing coproduction of the LHS as it is implemented, evaluated, and scaled through government funding.

Evidence Synthesis and Codesigning a LHS

The LHS was developed using a multistep codesign process including; engaging the national data-driven healthcare improvement committee across the centres and establishing leadership through the Monash Partners data governance committee with consumer and stakeholder input; obtaining resources through the Australian Government Medical Research Future Fund; and appointing a fellow (JE) and jointly agreeing on a vision and undertaking a rigorous process to develop the framework. We synthesized evidence on systematic review and qualitative research and completed workshops and consultations. The framework was codesigned with stakeholders, with coproduction in implementation and scale-up. Our stakeholders played an integral role throughout from foundational design, ongoing development, current implementation, embedding, and operationalizing the framework evaluating measurable health care improvement.

National governance was established through the data-driven healthcare improvement committee, and the initial priority setting process occurred with nominated members from each competitively accredited Research Translation Centre, consumers, and stakeholder representatives (9). Detailed methods and results of the systematic review and qualitative research are published elsewhere (7, 8) and summarized here.

Collective Vision and Evidence Collection

The codesign process involved multidisciplinary stakeholders including community, clinicians, academics, administrators, and industry and generated a collective vision of "Learning together for better health" to guide framework development.

Systematic Literature Review

The systematic review captured the academic and gray literature evidence on effective LHS (or similar entities with alternative names) that stimulated partnerships across multiple stakeholders and increased the translation of data and research in healthcare, with explicit evidence of health impact (8).

Forty-three articles were identified, which described research translation leading to impact in 23 LHS environments: United States ($n = 18$), Canada ($n = 2$), and one each in the UK, Sweden, and Australia/New Zealand. Key findings are summarized in **Box 1** and the full systematic review is published (8).

Qualitative Interviews

The expert panel and systematic review had informed the questions explored in the qualitative research. We purposively identified and conducted semistructured qualitative interviews with national and international leaders, including in the UK and Canada, experienced in supporting or developing data-driven innovations in healthcare (7). Representatives from all AHRA centres, Monash Partners member organizations, the Digital Health Collaborative Research Centre, State Government, Australian Digital Health Agency, Public Health Research Network, consumers and international experts from both the UK and Canada, were interviewed. Analysis of 26 interviews revealed

BOX 1 | Key findings of the LHS systematic review.

- Learning Health System environments are system level initiatives with effective examples demonstrating taking practice to data, integrating best practice evidence, undertaking data analysis to generate new knowledge, and implementing new knowledge back into clinical practice in an ongoing, systems level approach
- An integrated multidisciplinary team of frontline clinicians, researchers, and community members, embedded in healthcare settings is key to success
- To have direct health impact, a Learning Health System must provide timely access to data, as well as analysis of that data with feedback
- Effective Learning Health Systems require people with a broad range of workforce capacities to make sense of the data arising from complex healthcare environments

BOX 2 | Key themes that emerged from qualitative interviews on a learning health system.

- Structure, governance, trust, culture, vision, and leadership were all seen as important along with a skilled workforce and sustained investment
- Broad stakeholder, clinician and academic engagement, with collective vision, leadership, governance and a culture of trust, transparency, and co-design
- Resourcing with sustained investment over time
- Skilled workforce, capability, and capacity building
- Data access, systems, and processes
- Systematic approaches and iterative, continuous learning with implementation into healthcare contributing to new best-practice care to improve outcomes

five themes, integral to an effective, sustainable LHS, as shown in **Box 2**. Full details of the qualitative research are published (7).

Stakeholder Workshop

The expert panel and systematic review had informed the qualitative research, and learnings from these were integrated into a draft high-level framework and principles. This was followed by iterative stakeholder engagement *via* the members on the governance committee from partner organizations and finally within a stakeholder consultation workshop to refine the proposed model, ensuring adherence to the vision and alignment with end-user needs. The stakeholder consultation workshop was of 4 h duration and involved 60 representatives from Monash Partners organizations, government, national data agencies, AHRA centres, and consumers. It was facilitated by an experienced consultative facilitator. The workshop presented background and project findings, presentations by the state government chief information officer, and by academic clinicians who provided examples of effective LHS. Three of the authors (JE, HT, and AJ) presented the evidence gathered from the systematic review and qualitative interviews, as well as the related priorities established with these partner organizations in earlier related work (9). Immediately after a presentation on the draft LHS framework and principles, participants were divided into groups of ∼10 people per group and asked to provide input to refine the proposed draft framework. Each group workshopped at least one quadrant of the LHS framework with instructions to provide input to refine the model elements to improve alignment to the vision and end-user requirements. At the end of this session, a spokesperson from each group presented their inputs and suggestions for the LHS framework, and the facilitator supported the wider group to ask questions and make additional comments and/or suggestions for improvement. Written workshopped papers were collected by the researchers at the end of the workshop and transcribed into a report. Immediately after the workshop, two of the authors (JE and AJ) documented their key impressions arising from the discussions in the workshop by the participants and later incorporated this into the report. The feedback was incorporated into the LHS framework and sent out to participants electronically for comments, and further electronically iteratively refined to generate the final framework.

Monash Partners LHS

The final framework (**Figure 1**) encapsulates core phases across stakeholder-engagement and priority setting, integration of evidenced based best practice, taking routine health practice data from service delivery and patient care, analyzing this to generate new knowledge, and implementing this new knowledge back into practice in iterative cycles of data-driven healthcare improvement.

The framework is in the shape of a "circle" divided into four main quadrants (**Figure 1A**). Topics and functions for each quadrant are listed (**Figure 1B**). The framework shape and contents were synthesized using evidence from the systematic review, qualitative research, and consultation workshop.

The framework shows four key sources of evidence, with each represented diagrammatically in a quadrant of the LHS cycle (see **Figure 1**):

- Evidence of the stakeholder—from end user problems and priorities
- Research evidence—from primary research, evidence synthesis, and guidelines
- Data evidence—from practice data and data analysis, including artificial intelligence
- Implementation evidence—integrating rigorous implementation research into pragmatic healthcare improvement.

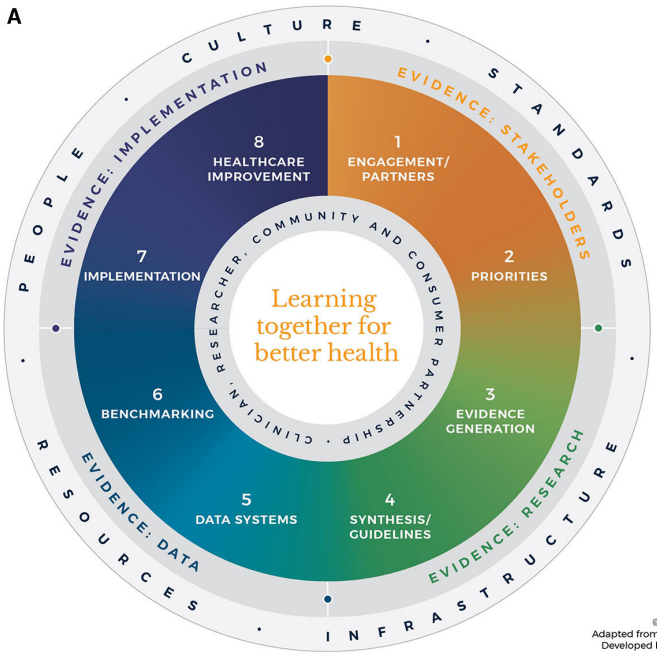
Each quadrant of evidence is vital to capture, identify, and address health service and community priorities and emergent challenges and needs to be integrated to create and operationalize the LHS as an iterative systems level intervention to deliver health impact.

DISCUSSION AND IMPLEMENTATION ACTIVITY

Our healthcare system faces a burgeoning aging population, rising complexity, rapid advances in technology, and escalating costs. Around 10% of healthcare is harmful, evidence is slow to implement, and system reform is challenging (1). Innovation to deliver quality and sustainable health system is vital, and methods are controversial and challenging. Here, we describe the codevelopment process of the framework to guide health care settings into becoming LHS. We present a rigorously developed LHS Framework grounded in NHMRC accredited Research Translation Centres (which are publically funded academic health science centres) with a mandate to integrate research into healthcare to deliver impact. The coproduced framework takes practice to data, data to new knowledge, and new knowledge to practice in a continuous learning cycle, to deliver evidence-based healthcare improvement and is currently being implemented and evaluated.

Whilst there are multiple different frameworks in use, most are derived from singular perspectives, be that a

A



© Monash University
Adapted from MCHRI framework
Developed by Monash Partners

B

COMPONENTS

STAKEHOLDER DERIVED EVIDENCE

1 ENGAGEMENT OF PEOPLE

- Consult
- Engage
- Involve
- Collaborate
- Empower
- Inform

2 IDENTIFYING PRIORITIES

- Formal engagement
- Agreed priorities
- Ranked priorities
- Prioritised outcome measures

RESEARCH DERIVED EVIDENCE

3 EVIDENCE BASED INFORMATION

- Cohort trials
- Randomised and pragmatic clinical trials
- Epidemiology based research
- Economic analysis
- Qualitative and Quantitative research

4 EVIDENCE SYNTHESIS AND GUIDELINES

- Systematic reviews
- Meta- analysis: aggregate and individual data
- Secondary research
- Consideration of stakeholder and evidence based priorities
- Guidelines, standards and policies

DATA DERIVED EVIDENCE

5 DATA AND INFORMATION SYSTEMS

- Quality, timely, harmonised, meaningful and actionable data
- Data from health care and other sources
- Patient reported experience and outcome measures
- Compliance with 5 safes*, FAIR data principles** and legislative and privacy requirements
- Governance, data sharing, linkage, analysis and interpretation
- Big data analytics, machine learning
- Technology and infrastructure

6 BENCHMARKING

- Transparency and equity
- Adjustments for service variation
- Real time visual representation at individual, service and organisational levels
- Measurement to iteratively and continuously drive improvement
- Evaluation
- Learning feedback

IMPLEMENTATION EVIDENCE

7 IMPLEMENTATION

- Leadership
- Theory driven
- Economically sound
- Methodologically rigorous
- Addressing barriers and enablers
- Capability in change management
- Consideration of the Burden of data collection
- Sustainable and scalable
- Demonstrating healthcare improvement

8 HEALTHCARE IMPROVEMENT

- Leadership
- Pragmatism
- Contextual/ local
- Outcome improvement
- Quality improvement
- Change management
- Evaluation

FIGURE 1 | (A) Monash Partners Learning Health System framework. The framework shows four key sources of evidence, with each represented diagrammatically in a quadrant of the Learning Health System cycle. **(B)** Bullet points list the topics and functions incorporated under each sub-section in the overarching LHS framework. The numbers correspond to the numbered sections in the LHS framework shown in **(A)**.

single health condition or an isolated research or healthcare perspective, and few consider the consumer and stakeholders as key to the system (2–6, 11–13). Given that current healthcare improvement strategies and conventional project-based approaches to transform care have been inadequate (1), a systems-level approach is required for sustainability and scalability. However, it is important that the LHS is broad and considers all dimensions of the complex adaptive system to succeed.

Frameworks for LHS have been described (2–6, 11–13), and each follows a similar cycle of assembling, analyzing, and interpreting data, followed by feeding the learnings back into practice and creating changes (2). We used this evidence-based process in Australia to develop the LHS framework through stakeholder engagement, and systematic review of LHSs that have delivered impact, qualitative interviews, and workshops contain the key components to succeed. Key components that emerged were evidence sources coming from stakeholders, data, implementation evaluation, and research.

There is clear support from both State and Federal Government health departments, for the LHS, with financial support for a number of projects. The Victorian state government has invested in the LHS in the Victorian healthcare recovery initiative to improve care delivery as we emerge from the COVID-19 pandemic (14). The processes involved engaging community, clinical networks, state government, and health service priorities including new evidence-based models of Telehealth and virtual care and reducing low-value care. Best practice evidence was sourced in these fields, including the Digital Health Cooperative Research Centre resources and the Choosing Wisely and Evolve low-value care initiatives (15). Practice data are being sourced and analyses and implementation are underway. This work is being evaluated at a project and LHS level. State Government funding is supporting data integration systems, and a process led by Monash Partners and a grant through the Medical Research Future Fund is supporting the development of data infrastructure within the LHS: "Towards a National Data Management Platform supporting Australia's Learning Health System." This initiative will utilize the LHS to support the implementation of a consistent approach to Data Sharing Agreements and Principles, modification, and utilization of systems that will support access to electronic medical records' unstructured data, across a number of health settings and will also link into interstate LHS initiatives through the AHRA network.

Monash Partners is now working across other Centres, partner organizations, Government, and stakeholders, and is funded to implement the LHS frameworks and pilot healthcare improvement projects to iteratively "learn together for better health."

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/cited material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This program of work was approved by the Monash University Human Research and Ethics Committee (Project ID: 19969).

AUTHOR CONTRIBUTIONS

HT, AJoh, AJon, and JE lead and participated in the project initiative at all key stages. JE and AJoh participated in data collection. AJoh, AJon, and HT facilitated the workshop. JE drafted the paper with guidance from AJoh, AM, AJon, and HT. All authors reviewed the draft manuscript, provided critical feedback with recommendations, reviewed and approved the final manuscript, conceptualized and designed the study, and participated in data analysis.

FUNDING

This work was supported by a fellowship program for one of the author (JE) from Monash Partners and funded by the Medical Research Future Fund.

REFERENCES

1. Braithwaite J, Glasziou P, Westbrook J. The three numbers you need to know about healthcare: the 60-30-10 challenge. *BMC Med.* (2020) 18:102. doi: 10.1186/s12916-020-01563-4
2. Melder A, Robinson T, McLoughlin I, Teede H. An overview of healthcare improvement: unpacking the complexity for clinicians and managers in a learning health system. *IMJ.* (2020) 50:1174–84 doi: 10.1111/imj.14876
3. McLachlan S, Potts HWW, Dube K, Buchanan D, Lean S, Gallagher T, et al. The heimdall framework for supporting characterisation of learning health systems. *J Innov Health Inform.* (2018) 25:77–87. doi: 10.14236/jhi.v25i2.996
4. Menear M, Blanchette MA, Demers-Payette O, Roy D. A framework for value-creating learning health systems. *Health Res Policy Syst.* (2019) 17:79. doi: 10.1186/s12961-019-0477-3
5. Flum DR, Alfonso-Cristancho R, Devine EB, Devlin A, Farrokhi E, Tarczy-Hornoch P, et al. Implementation of a "real-world" learning health care system: Washington State's Comparative Effectiveness Research Translation Network (CERTAIN). *Surgery.* (2014) 155:860–6. doi: 10.1016/j.surg.2014.01.004
6. Psek WA, Stametz RA, Bailey-Davis LD, Davis D, Darer J, Faucett WA, et al. Operationalizing the learning health care system in an integrated delivery system. *EGEMS.* (2015) 3:1122. doi: 10.13063/2327-9214.1122
7. Enticott J, Braaf S, Johnson A, Jones A, Teede HJ. Leaders' perspectives on learning health systems: a qualitative study. *BMC Health Serv Res.* (2020) 20:1087. doi: 10.1186/s12913-020-05924-w
8. Enticott J, Johnson A, Teede H. Learning health systems using data to drive healthcare improvement and impact: a systematic review. *BMC Health Serv Res.* (2021) 21:200. doi: 10.1186/s12913-021-06215-8
9. Teede HJ, Johnson A, Buttery J, Jones CA, Boyle DI, Jennings GL, et al. Australian Health Research Alliance: national priorities in data-driven health care improvement. *Med J Austr.* (2019) 211:494–7.e1. doi: 10.5694/mja2.50409
10. Robinson T, Skouteris H, Burns P, Melder A, Bailey C, Croft C, et al. Flipping the paradigm: a qualitative exploration of research translation centres in

the United Kingdom and Australia. *Health Res Policy Syst.* (2020) 18:111. doi: 10.1186/s12961-020-00622-9
11. Flynn A. Informatics and technology enable us to learn from every patient: Pharmacists' many roles in learning health systems. *Am J Health Syst Pharm.* (2019) 76:1095–6. doi: 10.1093/ajhp/zxz118
12. Budrionis A, Bellika JG. The learning healthcare system: where are we now? A systematic review. *J Biomed Inform.* (2016) 64:87–92. doi: 10.1016/j.jbi.2016.09.018
13. Ovretveit J, Nelson E, James B. Building a learning health system using clinical registers: a non-technical introduction. *J Health Organ Manag.* (2016) 30:1105–18. doi: 10.1108/JHOM-06-2016-0110
14. Centre; MPAHS. *Victorian Translation Centres Collaborative COVID-19 Healthcare Recovery Initiative*. (2020). Available online at: https://monashpartners.org.au/2020/06/12/victorian-translation-centres-collaborative-covid-19-healthcare-recovery-initiative/ (accessed October 15, 2020).
15. Soon J, Buchbinder R, Close J, Hill C, Allan S, Turnour C. Identifying low-value care: the Royal Australasian College of Physicians' EVOLVE initiative. *Med J Aust.* (2016) 204:180–1. doi: 10.5694/mja15.01398

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

POLICY AND PRACTICE REVIEWS
published: 17 November 2021
doi: 10.3389/fmed.2021.765385

Bridging the Gap: The Critical Role of Regulatory Affairs and Clinical Affairs in the Total Product Life Cycle of Pathology Imaging Devices and Software

Staci J. Kearney[1], Amanda Lowe[2], Jochen K. Lennerz[3], Anil Parwani[4], Marilyn M. Bui[5], Katy Wack[6], Gina Giannini[7] and Esther Abels[2]*

[1] Elevation Strategic Development, Morrison, CO, United States, [2] Visiopharm A/S, Horsholm, Denmark, [3] Department of Pathology, Massachusetts General Hospital/Harvard Medical School, Center for Integrated Diagnostics, Boston, MA, United States, [4] Wexner Medical Center, The Ohio State University, Pathology and Biomedical Informatics, Columbus, OH, United States, [5] Department of Pathology, Moffitt Cancer Center and Research Institute, Tampa, FL, United States, [6] PathAI, Boston, MA, United States, [7] Roche Tissue Diagnostics, Tucson, AZ, United States

OPEN ACCESS

Edited by:
Mira Pavlovic, NDA Advisory Services Ltd., United Kingdom

Reviewed by:
Lawrence Liberti, Temple University, United States
Segundo Mariz, European Medicines Agency, Netherlands
Domenico Criscuolo, Italian Society of Pharmaceutical Medicine, Italy

***Correspondence:**
Staci J. Kearney
stacijkearney@gmail.com

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *27 August 2021*
Accepted: *25 October 2021*
Published: *17 November 2021*

Citation:
Kearney SJ, Lowe A, Lennerz JK, Parwani A, Bui MM, Wack K, Giannini G and Abels E (2021) Bridging the Gap: The Critical Role of Regulatory Affairs and Clinical Affairs in the Total Product Life Cycle of Pathology Imaging Devices and Software. Front. Med. 8:765385. doi: 10.3389/fmed.2021.765385

Manufacturers of pathology imaging devices and associated software engage regulatory affairs and clinical affairs (RACA) throughout the Total Product Life Cycle (TPLC) of regulated products. A number of manufacturers, pathologists, and end users are not familiar with how RACA involvement benefits each stage of the TPLC. RACA professionals are important contributors to product development and deployment strategies because these professionals maintain an understanding of the scientific, technical, and clinical aspects of biomedical product regulation, as well as the relevant knowledge of regulatory requirements, policies, and market trends for both local and global regulations and standards. Defining a regulatory and clinical strategy at the beginning of product design enables early evaluation of risks and provides assurance that the collected evidence supports the product's clinical claims (e.g., in a marketing application), its safe and effective use, and potential reimbursement strategies. It is recommended to involve RACA early and throughout the TPLC to assist with navigating changes in the regulatory environment and dynamic diagnostic market. Here we outline how various stakeholders can utilize RACA to navigate the nuanced landscape behind the development and use of clinical diagnostic products. Collectively, this work emphasizes the critical importance of RACA as an integral part of product development and, thereby, sustained innovation.

Keywords: regulatory strategy, clinical affairs, total product life cycle, *in vitro* diagnostics development, digital pathology, business strategy, artificial intelligence, software development

INTRODUCTION

Pathology is the cornerstone of patient care, providing diagnostic, prognostic, and therapy-predictive information to a health care team. In the era of precision medicine and digital health, digital pathology tools and applications, including artificial intelligence (AI)-based applications, are enabling pathologists to deliver high-quality care to patients. However, more innovation is

needed. The delivery of high-quality care to patients continues to become more and more complex in the rapidly evolving age of digital health, personalized medicine, and value-based care. Digital pathology, both hardware and software, is no exception. Streamlining the regulatory process to get innovative digital tools into the hands of practicing pathologists is in the best interest of patients.

Manufacturers of pathology imaging devices and associated software should engage regulatory affairs and clinical affairs (RACA) professionals throughout the total product life cycle (TPLC) of these innovative medical devices. A significant number of manufacturers and end users (e.g., practicing pathologists), especially in the digital health space, are unfamiliar with the TPLC for regulated products, the role of RACA in the product development process, and the rigor of bringing a medical device to market. These manufacturers, as well as pathologists as the end users, can utilize RACA professionals to help navigate the nuances behind development and use of a regulated product.

Here we try to increase awareness of the importance of the role of RACA in delivering these products to practicing pathologists, administrators, and developers by the following:

- Demystify RACA by describing how the regulatory landscape shapes the delivery of clinical products
- Bridge the gap between the mindsets of the developer and the end user on the implementation of regulatory requirements and product features
- Establish a mutual vocabulary to facilitate understanding of the application of regulatory requirements

THE DYNAMIC REGULATORY ENVIRONMENT FOR DIGITAL PATHOLOGY

Regulatory trends and expectations for the approval process and post-market responsibilities shift and evolve, sometimes rapidly, particularly for advanced technologies like digital pathology. Digital pathology products, both hardware and software, are regulated as *in vitro* diagnostics (IVDs). From 2019 to 2020 alone, the US Food and Drug Administration (FDA) published more than 40 draft and final guidances that impact software, digital pathology, and IVD product development or approval [this does not include guidance specific to Coronavirus Disease 2019 (COVID-19)] (1). Also in 2020, members of Congress introduced the Verifying Accurate, Leading-edge IVCT Development (VALID) Act (2), which, if passed, will fundamentally change the regulation of diagnostic tests in the US. Similarly, the European Union (EU) introduced a transformative set of regulations for IVDs in 2017, with the entry into force of the *in vitro* diagnostic device regulation (IVDR) (3). Full compliance with the IVDR will be required in May 2022.

Transformational healthcare initiatives by regulatory bodies must also be considered. FDA's Digital Health Initiative outlines efforts to reimagine FDA's approach to ensuring timely access to high-quality, safe, and effective digital health products (4). It also encourages innovation and the facilitation of new approaches that support health care delivery and sharing of information. FDA is also a key participant in the Precision Medicine Initiative launched in January 2015 (5). Precision medicine, sometimes known as "personalized medicine," is an innovative approach to tailoring disease prevention and treatment that considers differences in people's genes, environments, and lifestyles. The goal of precision medicine is to target the right treatments to the right patients at the right time.

The success of precision medicine depends on having accurate, reproducible, and clinically useful diagnostic tests, including companion diagnostic (CDx) tests to identify patients who can benefit from targeted therapies. The diagnosis of breast cancer is a very good example. Four primary biomarkers are analyzed during the routine pathological work-up for breast cancer: estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and the proliferation-associated nuclear protein Ki67. Assessments of these biomarkers within collected tumor tissue (e.g., biopsy or surgical resection) are combined into surrogate subtype classifications, guiding conclusions about the tumor's biological characteristics and expected response to therapy. A comprehensive study conducted in 2016 by the Department of Clinical Pathology at Karolinska University Hospital in Stockholm, Sweden, demonstrated that image analysis performed on whole slide images (WSIs) of tissue on glass slides was superior to manual assessment and provided more prognostic information than the manual scores (6). The results of this study have been repeated numerous times, demonstrating that digital pathology products will be important for expanding the potential of diagnostic tests.

The complex and dynamic nature of medical device development requires engagement of multiple cross-functional disciplines. RACA professionals are an important contributor to product development and deployment strategies because they must maintain an understanding of the scientific, technical, and clinical aspects of a biomedical product, as well as deep knowledge of regulatory requirements, policies, and trends for both local and global regulations and standards. For this reason, it is recommended that RACA be involved very early in the TPLC to assist with navigating changes in the regulatory environment and the market. RACA can also optimize business processes for the TPLC through this knowledge sharing.

RACA DEFINED

RACA professionals work to design and promote a regulatory strategy that is aligned to the current regulatory landscape for a given clinical product or products. The strategy focuses on the efficacy and safety of the product(s), without sacrificing quality, and while ensuring an efficient time to market.

Regulatory affairs (RA) is often recognized for its role in communication with health authorities and overseeing regulatory submissions; however, RA's core competency is developing strategies that comply with both global and local regulations and standards, which are often moving targets. RA is also responsible for gathering and effectively applying regulatory intelligence throughout the TPLC, including pre-market and post-market strategies (**Table 1**).

TABLE 1 | Terminology defined: market environments.

Term	Definition
Regulatory intelligence	Information collected on the current regulatory environment and trends for an identified market.
Pre-market	A medical device is considered pre-market before it is offered commercially, which is typically during development. Review and clearance or approval of a marketing application is often required by a health authority for use in a clinical setting.
Post-market	A medical device is considered post-market when a manufacturer offers the product commercially. A product is marketed illegally if it is provided commercially without meeting applicable regulatory requirements.

A medical device is a regulated product regardless of whether it is used only for research or in a clinical setting.

Clinical affairs (CA) includes clinical science, strategy, and clinical operations; it is responsible for the generation and dissemination of sound scientific and clinical evidence, such as clinical study protocols, reports, and publications. Often, CA is key in defining clinical strategies that support a company's development objectives, while ensuring that products are designed according to a robust clinical evidence strategy. The generation of clinical evidence not only supports the product's introduction to the market, but also provides the foundation for establishing reimbursement strategies, which can drive the economic value of the product to the company. Carrying out successful clinical studies for development requires cooperation between CA and multiple functional groups, such as data managers, biostatisticians, business development, information technology, RA, research coordinators, product management/engineering, and many other functions.

While RA and CA have distinct responsibilities, these roles often overlap in the development of a product and in influencing and shaping the regulatory landscape. Importantly, RACA can bring together the developer and the user, including the patient, through external-facing roles that foster relationships that can be beneficial to the perception and adoption of the product. RACA can also assist with prioritizing markets based on the clinical and regulatory landscape, as well as ensure the correct intended use is identified and the supporting clinical evidence generated to align to the market environment. Overall, RACA provides a critical role in the product TPLC by applying clinical and regulatory strategies that can reduce business risk and product risk at all phases of development and commercialization.

RACA professionals' influence is often achieved through collaborations with regulatory bodies to drive policy and application of regulations, as well as through work to design and implement innovative approaches. To achieve this, RACA professionals are often contributors to technical committees, consortia, and trade organizations that work to accelerate standard development or to improve standards or guidelines to be more compatible with current technologies. For example, in 2016, the Digital Pathology Association's (DPA's) Regulatory and Standards Task Force played a major role in getting the device classification for WSI systems reclassified from an automatic Class III medical device that requires submission of a pre-market approval application (PMA) to a Class II device *via* a *de novo* request (7). The DPA and FDA closely collaborated on introducing consistency in terminology and developing general principles for test protocols that were acceptable to FDA. This close collaboration between regulators, healthcare workers, medical specialists, and industry represented a major shift in FDA's approach to WSI systems. Continued communication between FDA and digital and computational pathology-enabled organizations like the DPA, Association for Pathology Informatics (API), and the Pathology Innovation Collaborative Community (PIcc, formerly known as Alliance for Digital Pathology) is taking place to address AI-related products in pathology.

RECOMMENDATIONS ON THE USE OF RACA IN THE TPLC

Medical device development is often an iterative process; in general, it includes device discovery and concept, development, pathway to registration, commercialization, post-market surveillance, and end of life (**Figure 1**). RACA uses market and regulatory intelligence to work with product management and development teams to define clinical utilization, which provides clarity on the user requirements and formulation of the intended use, indications of use, and claim definitions. These descriptions then drive the device description, device classification, if applicable, and regulatory pathway.

Similarly, RACA engages clinical domain experts, who are users of the products, which often includes a collaboration with a field sales team. RACA can acquire input from users on product utility and function independently or with the help of product management. This is input is typically gathered through focus groups, surveys, and one-on-one interviews and is critical for ensuring a design that provides a safe, effective, commercially viable, and high-quality product. Additionally, this input, together with the state of the art of the product and comparison to standard of care, determines the benefit risk ratio used in submissions to regulatory authorities. While RACA professionals often seek out these clinical domain experts to receive their input, end users can engage the RACA professionals on the products they use typically through a customer support or sales channel of the product manufacturer.

Discovery and Concept

RACA can represent an aligning element in the product design and concept generation process. The design of a product should include screening the possible regulatory opportunities and risks based on a company's vision of a product and its geographical regions of deployment. This screening includes working within the product management and development team to identify opportunities, competition, development trends, and avenues for deployment. The screening process also provides an opportunity to develop insights for shaping the architectural design and intended use to suit most markets.

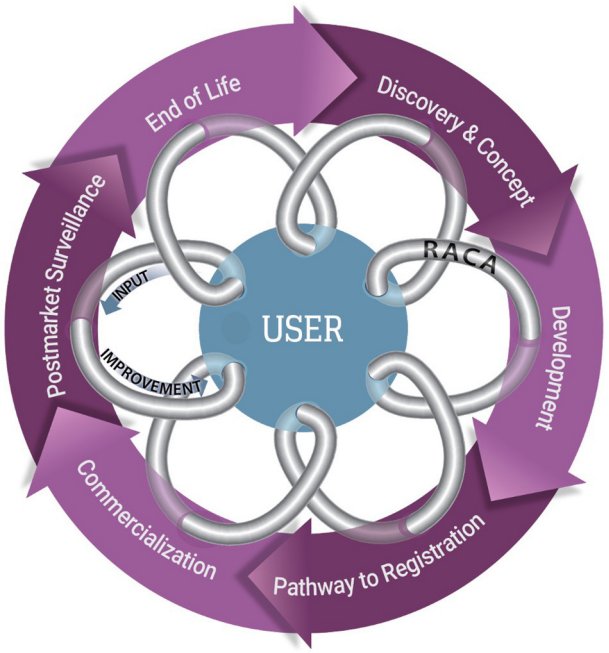


FIGURE 1 | The feedback loop for the TPLC for a commercialized clinical product. The TPLC for a commercialized clinical product, in general includes 6 primary steps that are often iterative in nature (purple circle). Manufacturers benefit from seeking input from users, such as pathologists and other healthcare providers, to continually introduce improvements and utility (arrows) into the product design. RACA professionals can be a conduit between users and industry (gray coil) to assist with delivering user input and communicating the implications of the changes.

To initiate the screening process, manufacturers must first generate a technical device description and architecture and then build requirements around the intended use according to the description. This intended use, technical device description, and architecture will drive the regulatory pathway and requirements needed to develop the product, which can vary from region to region. Using IVDs within the US and the EU as an example, device classifications, approval pathways, required supporting evidence, and post-marketing responsibilities differ. In the US, a medical device must comply with Code of Federal Regulations Title 21 Part 820 (21 CFR 820), under which medical devices and IVDs are not defined as separate (i.e., both are regulated under 21 CFR 820). However, in the EU, medical devices and IVDs are regulated under separate directives, the Medical Device Directive (MDD) 93/42/EEC and the *in vitro* diagnostic directive (IVDD) 98/79/EC, respectively. As of 2017, the EU entered into force the IVDR (2017/746/EC), which represents a large change from the previous directive (3). Under the IVDR, there are 4 IVD classifications (Classes A, B, C, and D), while medical devices in the US only have 3 classifications (Class I, Class II, and Class III). Using RACA professionals to understand how the requirements for each regulation are different and similar may allow a company to introduce efficiencies in development that meet both, while ensuring region-specific requirements are also met.

The interaction between RACA professionals and the commercialization team, including product management, sales, and marketing, is also essential at this early phase of product development to ensure that messaging and target markets are properly reached. This includes a profiling of the product to assess the overall product and business risks, which includes but is not limited to segmentation of the market, possible reach of market, the regulatory paths per target market, opportunities to obtain reimbursement including level of evidence required per market and related efforts and timelines. This profiling is an essential input for pricing and business models to enable the business to decide whether the product will be developed, brought to market (a so called "GO" or "NO GO" decision), and how it will be brought to the market.

Development

Device development is often an iterative process that includes refining or even changing a device design as the concept becomes a functioning prototype and then a finished device. Device design documentation is used to record the development process, usually by multiple stakeholders. This documentation relates to a series of development activities, including product requirements, market research, and customer input, as well as verification, validation, and clinical performance studies. Regulatory/health authorities often require products to meet certain specifications before the medical device can be deployed for its intended use.

While the specifics of development requirements can differ from region to region, the general principles of design control are a well-established and recognized standard. ISO 13485 is an internationally recognized standard that specifies requirements for a quality management system (QMS) to support the design and manufacturing of medical devices, including design controls (8). While the US has its own regulations that define requirements for design controls (21 CFR 820.30), they are highly similar to the internationally recognized principles (e.g., ISO 13485). However, it has been increasingly recognized that the design principles for software applications, such as for AI and machine learning (ML) applications for digital pathology, require a unique development approach that is more tailored to this type of technology. While the foundational design tenets are applied, software documentation, testing, traceability, and configuration management can be conducted and even scrutinized differently than non-software medical devices. International standards for software development exist [e.g., IEC 62304: Medical Device Software–Software Life Cycle Processes (9) and IEC 82304-1: Health Software (10)], but the landscape continues to evolve as the introduction of AI/ML-based software as a medical device (SaMD) and its applications rapidly expand.

In addition to a regulatory strategy, the requirements for clinical evidence should be identified early so worldwide clinical studies can be planned. Defining a clinical strategy at the beginning of product design allows for early evaluation of clinical risks and provides assurances that the clinical evidence could support validation of the product clinical claims in a marketing application. For manufacturers of digital pathology products, there are endless strategy and product design parameter combinations to consider: tissue, disease, biomarker, WSI digital

scanner, viewing system, and display, as well as the operational environment. To take each factor into consideration, the appropriate design of clinical studies requires a well-established network of collaboration within the biomedical field, such as with key opinion leaders (KOLs), who are often the end user of the product; contract research organizations (CROs); and development partners. Experienced RACA professionals can facilitate bringing these resources to the development process.

Pathway to Registration

National and international regulations provide guidelines to manufacturers regarding the regulatory pathway and registration procedures for medical devices, which must be followed prior to the sale and marketing of the device for diagnostic use in the intended clinical market. Within each global region, the regulatory pathway to device registration is defined by the classification of the device. For example, in the US, Class II medical devices are either cleared through a 510 (k) pre-market notification submission or a *de novo* request is granted (**Table 2**). Class III medical devices are approved through submission and review of a PMA application. All of these pathways have widely different requirements for evidence, including clinical evidence and documentation to support review of the submission. As previously noted, passing of the VALID Act will change the classification and approval process in the US, which will require significant preparation by manufacturers. Similarly, in the EU, an IVD's classification determines the appropriate conformity assessment procedure to follow and whether a notified body (NB) will be involved in the registration and certification process. The change in classifications in the IVDR dramatically increases the conformity requirements, and NBs will typically be more involved than in the past. For example, the burden of the TPLC for Class C and D devices is much higher than for Class A and B because these devices require at least annual updating of the performance evaluation report. As noted above, the intended use drives the device classification, and RACA input can be critical to ensuring the intended use language does not unintentionally place the device in a higher class than is needed for its clinical use. If this occurs, it could have a large impact on the business case for the product and cause the burden of development to exceed the market share or opportunity.

RACA professionals are becoming key members of the development team who assist with managing risk due to changing requirements. To de-risk the regulatory review process and understand expectations for evidence and documentation prior to submission of a marketing application, developers can seek feedback from FDA through the Pre-Submission Program (11). Within this program, a Q-Submission can be provided to FDA that includes a formal written request from a developer for feedback from FDA on development plans that is provided in the form of a formal written response or, if the submitter chooses, formal written feedback followed by a meeting in which any additional feedback or clarifications are documented in meeting minutes. Through these communications, a developer has the opportunity to obtain FDA feedback prior to submission of a marketing application. These communications are entirely voluntary on the part of the developer, but early interaction with FDA on planned non-clinical and clinical studies and careful consideration of FDA's feedback may improve the quality of subsequent submissions, shorten total review times, and facilitate the development process for new devices.

TABLE 2 | Terminology defined: US regulatory pathways.

Term	Definition
Cleared	FDA *clears* a medical device to be marketed after a manufacturer submits a 510 (k) marketing application and demonstrates substantial equivalency to a predicate device, as well as follows general controls, such as good manufacturing practices and special controls. This is a Class II medical device submission pathway.
De novo request granted	Manufacturers submit a *de novo* request (i.e., the marketing application) for Class II medical devices for which there is no predicate device. Upon review, FDA grants the request for the medical device to be a Class II device, and the medical device is considered cleared for marketing. This pathway is typically more rigorous than the 510 (k) pathway, but less rigorous than that for a Class III device.
Approved	Class III medical devices go through a rigorous and substantial review when manufactures submit a PMA application for FDA review. When a device is found to be safe and effective, FDA *approves* it for marketing.

Specific terminology defines which FDA submission pathway a medical device has gone through. For manufacturers, each term has implications for device development.

RACA typically takes the lead in organizing communications with regulatory bodies, including the strategy for how and when to gather information on a particular stage of development. A formalized program like FDA's Pre-Submission Program is less pronounced in other regions of the world but, in the EU, manufacturers can use engagement with NBs to understand certification requirements. NBs are required to be designated for IVDR to perform conformity assessments under this regulation. To date, there are only 6 designated NBs for IVDR (12), which is causing some concern among manufacturers as the May 2022 compliance date rapidly approaches. RACA professionals are often responsible for contracting with NBs and, even more importantly, are responsible for making well-informed decisions about the concepts, content, and specific language used in an application based on the different policies and processes defined by each NB. This requires development of strong relationships with an NB and use of regulatory domain knowledge to incorporate technical and clinical information into an application for review. Therefore, RACA represents the gateway to the competent authorities.

An additional pathway to entry to the clinical market that is unique to IVDs is offering a clinical test as a laboratory developed test (LDT). An LDT is defined as a diagnostic that is designed, manufactured, and used within a single laboratory (13). In the US, LDTs can be offered as clinical tests under the Clinical Laboratory Improvement Amendments (CLIA) regulations without having gone through FDA clearance or approval (14). Numerous advanced diagnostics, such as next generation sequencing (NGS), flow cytometry, polymerase chain reaction (PCR), and histopathology image analysis applications,

have been introduced into clinical use by this pathway. The COVID-19 public health emergency (PHE) highlighted the agility of this pathway. In March 2020, a Memorandum issued by the White House reversed FDA's position that all COVID-19 diagnostic tests must undergo an Emergency Use Authorization (EUA) review and approval by FDA, and instead allowed independent authorization of LDTs by states (15). This reversal was likely due to a need for expediency in the availability of and access to these tests in unprecedented circumstances and FDA's limited resources to handle the onslaught of submissions. However, controversy has long existed about the enforcement discretion FDA has applied to the regulation of LDTs. The introduction of the VALID Act will formally define the regulation of LDTs by FDA, which will require these types of developers to establish a compliant QMS and be subject to pre-market review, when applicable, for all tests offered for clinical use. Similarly, the new IVDR increases restrictions on the ability to offer LDTs in the EU.

Commercialization

Approval/clearance of a regulatory submission or successful registration allow for commercial introduction into the clinical market but represents only the first step in the adoption of a product. A customer will adopt innovation more easily when the return on investment (ROI) is proven, and ROI can be influenced by payer reimbursements. This increases the need for early identification of reimbursement and other incentives for ROI for users and manufacturers. An example of using RACA experts to optimize the go-to-market strategy is leveraging their knowledge of health authority programs that can benefit product commercialization. FDA's Breakthrough Device Designation (BDD) program (16) is a voluntary program for certain devices that provides manufacturers prioritized review of a submission, shortening the time to market, and potentially as a benefit for reimbursement strategies based on the Medicare Coverage of Innovative Technology (MCIT) rule (17). While the process of obtaining reimbursement is outside the scope of this paper, it is valuable to use a RACA professional's unique knowledge and experience to provide insights about how to utilize regulatory intelligence and device information, such as the intended use, indications of use, claims, and clinical safety, within a commercialization strategy (**Table 3**).

Labeling is also an important component of commercialization, which is actually a very broad term. Labeling can include instructions for use (IFU), packaging, all forms of advertisement, and any external communications or descriptions of the device. Labeling materials are typically generated by engineers and products teams, but RACA provides important input on the boundaries of labeling. For example, it is advisable for RACA to review all external communications that discuss the product, even those that might seem unrelated, such as an investor presentation. Word choice and descriptions

TABLE 3 | Terminology defined: regulated product information.

Term	Definition
Intended use /indications of use	Statements in the labeling that describe the purpose of the device, including the disease or condition for which the medical device can be used. Health authorities review and determine the appropriateness of these statements for inclusion in medical device labeling. The use of the medical device will be limited to the context of these statements.
Labeling	The information that identifies and describes a medical device. This can include the stickers or tags on the physical device, but also includes the instructions for use (IFU), which define how, when, and by whom a medical device can be used.
Claim	A statement about the safety, efficacy, or use of a medical device. Health authorities will only allow manufacturers to make claims that have been proven in marketing applications by evidence.

The scope and context of use of a medical device are defined by a manufacture and captured in the device information. Health authorities review this information to determine its appropriateness based on the evidence provided, and the medical device use is then limited to the defined information.

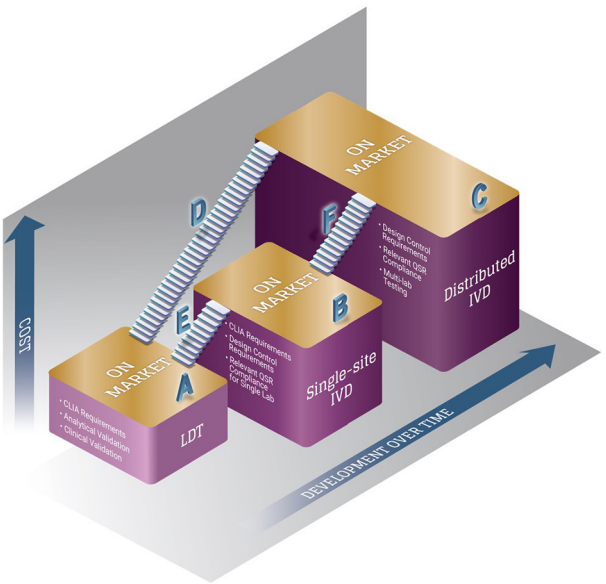


FIGURE 2 | Multiple pathways exist for bringing a clinical diagnostic product to market in the US. The introduction of a clinical diagnostic product on the market can proceed through multiple pathways. As straight-to-market strategies (A, B, C), manufacturers who also have laboratories (e.g., CLIA-certified lab) can choose to introduce a diagnostic test as an LDT, which is currently regulated under CLIA (A) or as a single-site IVD, which undergoes FDA review (B). Manufacturers intending to distribute a diagnostic for broad use by clinical laboratories must complete multi-lab testing and usually represents the greatest compliance requirements, but also greatest access (C). A stepwise approach can also be utilized by manufacturers who have laboratories as a de-risking strategy of reaching multiple on-market milestones along the commercialization pathway (D, E, F). A clinical diagnostic test first offered as an LDT can then be further developed directly as a distributed IVD (D), or first developed with increasing requirements to undergo FDA review as a single-site IVD (E), and then further development for a distributed IVD (E + F). Some LDTs are only offered as a single-site IVD as a second milestone (E), which is typical for advanced diagnostics. Similarly, products first offered as a single-site IVD can then be further developed as a distributed version (F). Each approach has pros and cons and differing associated requirements, and the cost and development timeline for each approach should be considered in evaluating the pros and cons.

must be considered carefully to prevent false advertising of the product that could unintentionally trigger consequences from regulatory authorities. RACA input can also be critical when determining how labeling can influence market positioning. For IVDs, products in the laboratory research phase can be labeled for research use only, making them exempt from most regulatory requirements, including pre-market requirements and/or applications (18). However, any reference to clinical claims or use could cause a product to become subject to regulatory oversight, which impacts sale and distribution of the product. RACA should be used to ensure this boundary is not inadvertently crossed. Gathering this input in the early phases of the TPLC can help optimize the approach for initial market entry of a product and beyond (**Figure 2**).

Post-market Surveillance

A manufacturer's responsibility for monitoring safety in the use of a product does not end after the product's validation and approval/clearance/registration. The safe use of a medical device must be continuously monitored, and when indicated, the product must be recalled or redesigned to improve the safety profile. To increase the discovery of adverse events in the general population, FDA created a safety information and adverse event reporting service (AERS) called MedWatch. MedWatch is a voluntary reporting system for consumers, patients, and health professionals that allows for safety surveillance of medical devices, as well as other FDA-regulated products (19). The Manufacturer and User Facility Device Experience (MAUDE) database is an additional system for monitoring safety (20). MAUDE houses medical device reports submitted to FDA by mandatory reporters, including manufacturers, importers, and device user facilities. Reporting through these systems can sometimes lead to initiating a voluntary or involuntary recall of a product and/or additional testing, including a potential clinical study to determine if product changes are needed. It is recommended that RACA professionals take the lead in executing both activities.

Requiring commitments to conduct clinical studies in the post-market is an approach regulators can use to support continued approval of a product. For example, as a condition of approval, FDA can include a post-market commitment to conduct additional studies. These studies are often used to allow expedited access to a product, while continuing to gather information on its performance. Post-market studies also provide significant commercial value to support ROI and improvements made to a medical device. This approach has been applied with increasing frequency, particularly for expedited approval pathways, such as for the devices that receive a BDD from FDA. FDA grants a BDD for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. It is available for devices and device-led combination products that are subject to PMA, 510 (k), or *de novo* request review. The BDD program is intended to help patients have more timely access to these medical devices by expediting their development, assessment, and review, while preserving the statutory standards for authorization (16). This path could be extremely beneficial when a device will be used as a CDx for a drug that has been granted accelerated approval. The first digital pathology BDD was issued in 2019 (21).

In certain regions, post-market studies can also be a requirement for any marketed clinical product. In the EU, manufacturers are required to establish post-market surveillance (PMS) plans to comply with the IVDR. The IVDR states that manufacturers must play an active role in gathering information in a way that allows for regular updates to technical documentation, including Post-market Performance Follow-up (PMPF) studies. Using RACA experts early in the TPLC will help to identify the least burdensome approach for the PMPF.

End of Life

End of life for a product could be represented by retirement of an obsolete technology or, more commonly, change and improvement to an existing device that represents the next generation and eventual retirement of the previous version. For the latter, manufacturers have important considerations and requirements when applying changes and introducing an improvement, update, or even more substantial change to a medical device currently on the market. Specifically, a manufacturer must determine how to support previous versions of a medical device when a new version is introduced. These devices must be phased out appropriately to avoid interruptions in patient care for customers still utilizing the technology. This is also an important business consideration when the medical device is being used as a CDx. Once the drug is on the market, it could remain there forever and, if indicated, the CDx must continue to support the drug use. This could be challenging for devices that require frequent updates, such as SaMDs types of devices, and remaining compatible with rapid evolving technology could have business impacts.

Important consideration also must be given to how a new version of an existing product is introduced to the market, which will likely have requirements for additional regulatory submissions and, potentially, analytical and/or clinical studies. RACA professionals can assist with understanding

TABLE 4 | Product codes and descriptions for digital pathology devices.

Product code	Description	Regulatory number
OEO	Automated digital image manual interpretation microscope	21 CFR 864.1860
NQN	Microscope, automated, image analysis, immunohistochemistry, operator intervention, nuclear intensity, and percent positivity	21 CFR 864.1860
NOT	Microscope, automated, image analysis, and operator intervention	21 CFR 864.1860
PSY	Whole slide imaging system	21 CFR 864.3700
PZZ	Digital pathology display	21 CFR 864.3700
QKQ	Digital pathology image viewing and management software	21 CFR 864.3700

TABLE 5 | FDA cleared digital pathology devices within the last 10 years.

510 (k) number*	Product	Product code**	Approval date (mm/dd/yyyy)
K111543	VIRTUOSO (TM) System for IHC HER2 (4B5)	OEO; NOT	10/12/2011
K111755	VIRTUOSO System for IHC KI-67 (30-9)	OEO; NQN; NOT	02/22/2012
K111869	VIRTUOSO System for IHC PR (IE2)	OEO; NQN	03/05/2012
K111872	VIRTUOSO System for IHC P53 (DO-7)	OEO; NQN; NOT	04/19/2012
K111914	Virtual Slide System Olympus VS800 System	OEO	08/21/2012
K121033	VIRTUOSO System for IHC KI-67 (30-9)	OEO; NQN; NOT	09/6/2013
K121350	VIRTUOSO System for IHC (DO-7)	OEO; NQN; NOT	06/01/2012
K121516	VIRTUOSO System for IHC HER2 (4B5)	OEO; NQN; NOT	09/26/2013
K122143	VIRTUOSO System for IHC PR (1E2) Benchmark Ultra Stainer	OEO; NQN; NOT	09/19/2013
K130021	Philips Herceptest Digital Score	OEO	09/19/2013
K130515	VIRTUOSO System for IHC ER (SPI)	OEO; NQN; NOT	11/22/2013
K131140	Omnyx IDP for HER2 Manual Application	OEO	04/01/2014
K140465	VIRTUOSO System for IHC ER (SP1) with Benchmark Ultra Stainer	OEO; NQN; NOT	03/20/2014
K140957	Genasis HIPATH IHC Family	NQN; NOT	01/15/2015
K141109	Aperio EPATHOLOGY EIHC IVD System	NQN; NOT	07/29/2014
K142965	Virtuoso System for IHC PR (1E2) using iScan HT	OEO	70/16/2015
K172174	Philips IntelliSite Pathology Solution	PSY	10/04/2017
K172922	Barco N.V. MMPC-4127F1 (PP27QHD)	PZZ	12/21/2017
K190332	Aperio AT2 DX System	PSY	05/20/2019
K192259	Philips IntelliSite Pathology Solution	PSY	09/20/2019
K193054	Sectra Digital Pathology Module	QKQ	03/31/2020
K201005	FullFocus	PSY; QKQ	07/15/2020

**The information listed in this table was collected through searches of FDA's 510 (k) database.*
***The list is limited to the 6 product codes listed in **Table 4**.*

when a product change has regulatory implications, which can differ depending on the technology and type of change. For example, FDA recognized in a recently published discussion paper that AI-based SaMD algorithms, which include those for digital pathology applications, should have appropriately tailored regulatory oversight to prevent unnecessary barriers to access to innovation (22). This discussion paper proposes potential approaches that could decrease certain requirements for submissions due to device changes in the post-market, such as approval of pre-determined change-control plans that include SaMD pre-specifications and an algorithm change protocol. FDA subsequently published an action plan for AI/ML-based SaMDs that outlines the actions FDA will take to develop this framework (23). Given the changing nature of the regulatory landscape for innovative technologies in the post-market and varying requirements for different technologies, RACA professionals can be vital to product teams in supporting product updates.

DISCUSSION

Digital pathology is relatively new to clinical diagnostic pathology, but the technology has been used extensively for research over the past 20 years (24). The safety of patients and the quality of the pathology results are critical to the practice of pathology, which is highly controlled by various regulatory bodies. However, it should be noted that pathology as a medical practice is not under the authority of a regulatory body. Based on the intended use of digital pathology devices to date, whole slide scanners, viewers, image management systems (IMSs), and algorithms are classified as one or more types of medical devices (**Table 4**). Numerous digital pathology devices have been cleared in the last few decades, including more than 20 devices over the last 10 years (**Table 5**).

In January 2021, a Federal Register (FR) Notice was published suggesting that certain Class I and Class II devices should receive permanent exemption from certain pre-market notification requirements, which included 4 product codes associated with digital pathology products: OEO, PSY, PZZ, QKQ (25). While this FR Notice was ultimately withdrawn in April 2021, citing insufficient information to broadly grant such exemptions (26), this presented a unique opportunity to continue discussions between regulators, industry, and users as multiple public comments to the docket supported a reexamination of the regulatory requirements for digital pathology products. Specifically, the interoperability of the components of these devices, the technical performance assessments, and evidence and studies necessary to bring a product to market now warrant a re-evaluation with the additional experience and new information available on the use of these products. For example, the COVID-19 PHE has presented a unique opportunity to observe the interoperability of certain digital pathology systems in a real-world setting as a result of FDA's guidance enabling the remote use of digital pathology systems that have not undergone 510 (k) pathway clearance (either as a new device or modification

to an existing device) for this intended use (27). Industry-leading organizations, such as the DPA, API, and the PIcc continue to engage regulatory bodies in communication on the right-sized requirements needed to introduce digital pathology products to the market to ensure regulation keeps pace with innovation. However, it should also be noted that adoption, not just access, requires additional effort by the field to increase utilization of these practice-enhancing technologies.

This review has outlined several key aspects related to RACA's involvement in TPLC management for digital pathology and AI/ML tools, with the primary aim to establish a common vocabulary to improve communication between the healthcare industry and pathology practice. For industry, the goal was to advocate for increased awareness that many practicing pathologists may be overburdened with the nuanced regulatory terminology. For pathologists, the goal was to help increase understanding of RACA and detangle some of the complexity surrounding it. RACA ultimately bridges the gap between the manufacturers and end users of medical devices, playing a critical role in the TPLC by synthesizing the various components, value propositions, and commercialization of regulated digital pathology solutions in a safe, efficient, and value-based manner.

AUTHOR CONTRIBUTIONS

All authors contributed to manuscript generation, revision, read, and approved the submitted version.

ACKNOWLEDGMENTS

The authors thank the Digital Pathology Association (DPA) for the support in the generation of this article.

REFERENCES

1. FDA Medical Devices Database. *Search for FDA Guidance Documents*. Available online at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch (accessed August 26, 2021).
2. Congress. *VALID Act of 2020*. (2020). Available online at: https://www.congress.gov/bill/116th-congress/senate-bill/3404/text (accessed June 5, 2021).
3. Official Journal of the European Union. *Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro Diagnostic Medical Devices and Repealing Directive 98/79/EC and Commission Decision* 2010/227/EU. OJ L 117, 5.5.(2017). p. 176–332.
4. US Food & Drug Administration. *Digital Health Center of Excellence*. Available online at: https://www.fda.gov/medical-devices/digital-health-center-excellence (accessed August 26, 2021).
5. Obama White House. *The Precision Medicine Initiative*. Available online at: https://obamawhitehouse.archives.gov/precision-medicine (accessed June 1, 2021).
6. Stålhammar G, Fuentes Martinez N, Lippert M, Tobin NP, Mølholm I, Kis L, et al. Digital image analysis outperforms manual biomarker assessment in breast cancer. *Mod Pathol*. (2016) 29:318–29. doi: 10.1038/modpathol.2016.34
7. DPA Press Release. *Digital Pathology Association Stands Behind the FDA's Approval of Marketing Whole Slide Imaging System*. (2017). Available online at: https://digitalpathologyassociation.org/41317-dpa-stands-behind-the-fdas-approval-of-marketing-whole-slide-imaging-system (accessed May 24, 2021).
8. International Organization for Standardization. *Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes (ISO Standard No. 13485:2016)* (2016). Available online at: https://www.iso.org/standard/59752.html
9. International Electrotechnical Commission 210. *Medical Device Software – Software Life Cycle Processes – Amendment 1. Edition 1.1. (ISO Standard No. 62304:2006/AMD 1:2015)* (2015). Available online at: https://www.iso.org/standard/64686.html
10. International Electrotechnical Commission 215. *Health Software - Part 1: General Requirements for Product Safety. (ISO Standard No. 82304-1:2016)* (2016). Available online at: https://www.iso.org/standard/59543.html
11. US Food & Drug Administration. *Requests for Feedback and Meetings for Medical Devices Submissions*. The Q-submission Program; Guidance for Industry and Food and Drug Administration Staff (2021). Available online at: https://www.fda.gov/media/114034/download
12. European Commission. *Notified Bodies Nando. Regulation (EU) 2017/746 on in vitro Diagnostic Medical Devices*. Available online at: https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=35 (accessed August 26, 2021).
13. US Food & Drug Administration. *Laboratory Developed Tests*. Available online at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests (accessed May 24, 2021).
14. Centers for Medicare & Medicaid. *LDT and CLIA FAQs*. Available online at: https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf (accessed June 1, 2021).
15. *2020-05793: Expanding State-Approved Diagnostic Tests; Memorandum for the Secretary of Health and Human Services*. Available online at: https://www.federalregister.gov/documents/2020/03/18/2020-05793/expanding-state-approved-diagnostic-tests (accessed April 16, 2021).
16. US Food & Drug Administration. *Breakthrough Devices Program*. Guidance for Industry and Food and Drug Administration (2018). Available online at: https://www.fda.gov/media/108135/download
17. *CMS-2020-0098: Medicare Program; Medicare Coverage of Innovative Technology (MCIT) and Definition of "Reasonable and Necessary"*. Available online at: https://www.federalregister.gov/documents/2021/01/14/2021-00707/medicare-program-medicare-coverage-of-innovative-technology-mcit-and-definition-of-reasonable-and (accessed March 28, 2021).
18. US Food & Drug Administration. *Distribution of in vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only*. Guidance for Industry and Food and Drug Administration Staff (2013). Available online at: https://www.fda.gov/media/87374/download
19. *FDA Webpage: MedWatch: The FDA Safety Information and Adverse Event Reporting Program*. Available online at: https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
20. US Food & Drug Administration. *MAUDE – Manufacturer and User Facility Device Experience*. Available online at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm (accessed April 16, 2021).
21. Paige.AI Press Release, March 07, 2019. *FDA Grants Breakthrough Designation to Paige.AI*. Available online at: https://www.paige.ai/resources/fda-grants-breakthrough-designation-to-paige.ai (accessed May 24, 2021).
22. US Food & Drug Administration. *Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD); Discussion Paper and Request for Feedback*. (2019). Available online at: https://www.fda.gov/media/122535/download (accessed January 21, 2021).
23. US Food & Drug Administration. *Artificial Intelligence/Machine Learning (AI/ML)-based Software as a Medical Device (SaMD) Action Plan*. (2021). Available online at: https://www.fda.gov/media/145022/download (accessed August 11, 2021).
24. Pantanowitz L, Sharma A, Carter AB, Kurc T, Sussman A, Saltz J. Twenty years of digital pathology: an overview of the road travelled, what is on the horizon, and the emergence of vendor-neutral archives. *J Pathol Inform*. (2018) 9:40. doi: 10.4103/jpi.jpi__18

25. RIN 0991-ZA52: *Making Permanent Regulatory Flexibilities Provided During the COVID-19 Public Health Emergency by Exempting Certain Medical Devices from Premarket Notification Requirements.* Available online at: https://www.federalregister.gov/documents/2021/01/15/2021-00787/making-permanent-regulatory-flexibilities-provided-during-the-covid-19-public-health-emergency-by (accessed April 16, 2021).
26. RIN 0991-ZA52: *Making Permanent Regulatory Flexibilities Provided During the COVID-19 Public Health Emergency by Exempting Certain Medical Devices from Premarket Notification Requirements; Withdrawal of Proposed Exemptions*. Available online at: https://www.federalregister.gov/documents/2021/04/16/2021-07760/making-permanent-regulatory-flexibilities-provided-during-the-covid-19-public-health-emergency-by (accessed April 16, 2021).
27. US Food & Drug Administration. *Enforcement Policy for Remote Digital Pathology Devices During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency. Guidance for Industry, Clinical Laboratories, Healthcare Facilities, Pathologists, and Food and Drug Administration Staff* (2020). Available online at: https://www.fda.gov/media/137307/download

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 23 December 2021
doi: 10.3389/fmed.2021.795659

The Role of EUPATI CH in Promoting Patient Involvement in Clinical Research: A Multi-Stakeholder Research Project

Cristiana Sessa[1], Caecilia Schmid[2], Angela Tolotti[3], Annette Magnin[2], David Haerry[4], Loris Bonetti[3] and Ingrid Klingmann[5]*

[1] Department of Medical Oncology, Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland, [2] Swiss Clinical Trial Organisation (SCTO), Bern, Switzerland, [3] Department of Nursing, Research and Development Unit, Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland, [4] Positive Council Switzerland, Zurich, Switzerland, [5] European Forum for Good Clinical Practice (EFGCP), Brussels, Belgium

OPEN ACCESS

Edited by:
Steffen Thirstrup, NDA Advisory Services Ltd, United Kingdom

Reviewed by:
Helen Baker, Moorfields Eye Hospital NHS Foundation Trust, United Kingdom
Domenico Criscuolo, Italian Society of Pharmaceutical Medicine, Italy

***Correspondence:**
Cristiana Sessa
cristiana.sessa@eoc.ch

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *15 October 2021*
Accepted: *07 December 2021*
Published: *23 December 2021*

Citation:
Sessa C, Schmid C, Tolotti A, Magnin A, Haerry D, Bonetti L and Klingmann I (2021) The Role of EUPATI CH in Promoting Patient Involvement in Clinical Research: A Multi-Stakeholder Research Project. Front. Med. 8:795659. doi: 10.3389/fmed.2021.795659

Background: The European Patients' Academy on Therapeutic Innovation Switzerland (EUPATI CH) was established as an association in 2016 with the mission to improve patient empowerment in Switzerland, raise public awareness of EUPATI's education material, and foster multi-stakeholder partnerships in order to promote public involvement in all aspects of medicines research and development (R&D). In order to achieve its goal of improving patient involvement (PI) in all processes of medicines R&D in Switzerland and to obtain guidance and recommendations for future activities, EUPATI CH initiated a multi-stakeholder survey on PI experiences, hurdles, and best practices. The survey enabled EUPATI CH to obtain and analyze the views of various stakeholders and shape its workplan.

Methods: Data collection occurred between January and July 2019 using a survey and semi-structured interviews with individual stakeholders from different groups. The online survey responses were analyzed using quantitative methods and the interviews were analyzed using qualitative methods.

Results: The online survey was completed by 55 respondents (10%), and the semi-structured interviews were conducted with 14 stakeholders. Respondents to the online survey were patient representatives (45%), researchers from academia (25%), individuals from the pharmaceutical industry (9%), healthcare professionals (23%), and representatives from government agencies (6%). Some respondents were also members of EUPATI CH. Thirty-eight percent of respondents consider PI in Switzerland to be limited or absent. They identified the main barriers to PI as, first and foremost, a lack of funds and human resources (65%), followed by a lack of information and a lack of education on how to become a patient advocate (21%), a lack of collaboration with other stakeholders (16%), and a lack of adequate resources. Respondents' expectations of EUPATI CH's role in supporting PI were to provide education for active PI and improve networking and collaboration among stakeholders.

Conclusions: EUPATI CH's multi-stakeholder research identified some of the difficulties in promoting PI in medicines R&D in Switzerland, in particular the complex collaboration among stakeholders and a lack of funds, human resources, and knowledge. To respond to these difficulties, EUPATI CH has begun preparing a basic training course for patients that is adapted to Switzerland.

Keywords: patient involvement, patient engagement, medicines research and development, drug development, EUPATI, patient representatives, training

INTRODUCTION

Patient involvement (PI) is generally recognized as being valuable when planning health policies that aim to increase their relevance for patients and healthcare. PI has the potential to improve the quality and safety of the healthcare services provided and to increase their value to patients.

There are different ways patients can contribute beyond mere participation, namely as advisors or partners in healthcare research. Besides ethical and political arguments such as democracy and empowerment, there are convincing arguments for the value of PI and patient and public involvement (PPI) in enhancing the relevance, validity, quality, and success of health research.

Involving patients in research can also benefit the medicines development process: bringing in patients' priorities and perspectives can contribute to the development of better treatments for participants and other patients with a particular disease. More active and extensive PI in the medicines R&D process can improve the safety and efficacy of new treatments and can increase the public's awareness of and participation in medical research (1, 2).

The European Medicines Agency (EMA) has been a driver of PPI since 2000. For example, the EMA includes patients in different medicines evaluation committees such as the Committee for Orphan Medicines (COMP) and it promotes the involvement of patients as critical stakeholders in the regulatory process. Over the years, the EMA has developed extensive collaboration with patients and consumer representatives.

The pharmaceutical industry has also recognized the value of integrating patients' contributions into the medicines development, regulatory, and licensing processes; however, it has suffered from a limited availability of patients who are knowledgeable in the relevant methodologies. The Innovative Medicines Initiative (IMI), a public-private partnership between the European Union—represented by the European Commission—and the European Federation for Pharmaceutical Industries (EFPIA), has recognized and supported the need for educating patients on medicines development methodologies and has sought their active involvement as partners in IMI-funded projects. From 2012 to 2017, the IMI ran a pan-European, patient-led project involving 33 public and private organizations with the aim of increasing the education level of patients. This initiative was called the European Patients' Academy on Therapeutic Innovation (EUPATI) project. The main aim of the IMI-EUPATI project was to educate patients using a diploma-type blended learning course and a large toolbox with information material in the seven most spoken languages (3). The EUPATI consortium included patient organizations, academic groups, non-profit organizations, and pharmaceutical companies, and its objectives were to develop and disseminate accessible, well-structured, scientifically reliable educational material for patients that is related to the process of medicines R&D—from the pre-clinical phase to post-marketing. Other topics related to these processes, such as personalized medicine, efficacy and safety assessment, risk-benefit assessment and risk-benefit ratio, health economics, health technology assessment (HTA), and PI were also included. The sustainability plan required by the IMI was successfully implemented in the form of the recently established EUPATI Foundation, which is based in the Netherlands.

EUPATI's concept was based on the experience of HIV and oncology patient communities, in particular the understanding that a better grasp of medicines R&D processes allows patient experts and advocates to work more effectively with the relevant authorities, healthcare professionals, and the pharmaceutical industry—and thus provide valuable input to the medicines development process for the benefit of all patients. Patient experts in patient organizations can become important advocates and advisors in medicines R&D. Gaining relevant expertise can empower patients to provide patient-focused advice and their personal opinions to pharmaceutical industries, academia, authorities, and ethics committees.

In addition to providing training material in the EUPATI Toolbox in now 13 languages, the IMI-EUPATI project has resulted in the establishment of 23 EUPATI National Platforms (ENPs) to date that drive patient education at the national level.

The EUPATI National Platform in Switzerland was established in 2012. In 2016, it was transformed into the association EUPATI CH, with the mission to improve patient empowerment in Switzerland, raise public awareness for EUPATI's education material, and foster multi-stakeholder events to discuss the best pathways for public involvement in all aspects of medicines R&D. In order to achieve its goal of improving PI, to better understand the stakeholders' needs, and to develop guidance and recommendations for the future activities, EUPATI CH started a multi-stakeholder research project in 2019 with semi-structured interviews and a survey. The results of the interviews and survey are reported in this article.

METHODS

Aims

The overall aim of this multi-stakeholder research project was to obtain guidance and recommendations for EUPATI CH on how to achieve its goal of promoting patient involvement in medicines R&D. Further aims were to identify relevant stakeholders, obtain information about ongoing activities related to PI in Switzerland, identify factors that affect PI, and obtain feedback on the role EUPATI CH can play in improving the impact of PI in the future.

Study Design

The first steps were to categorize EUPATI CH stakeholders by identifying relevant groups (patients and patient organizations, policymakers and regulators, academia, the pharmaceutical industry, and healthcare professionals) (**Appendix 1**) and define EUPATI CH's role in PI in medicinal R&D in Switzerland. Stakeholder categories were defined according to the classification of Deverka et al. with some modifications to take into consideration Swiss legislation and the Swiss healthcare system (4).

Study Population

Stakeholders were categorized based on the information available on their websites or in published material available from their institution or organization. The subsequent step was to establish direct contact with stakeholders to determine their level of knowledge of patient involvement. This was first done by an online survey with target people drawn from lists of existing contacts (EUPATI CH members, participants at EUPATI CH events, and others) according to a convenience sampling (5).

The next step was a personal, semi-structured interview. Interviewees were selected based on a purposing sampling method (6), targeting individuals within each of the five stakeholder groups (patients and patient organizations, health policymakers and regulators, academia, the pharmaceutical industry, and healthcare professionals) who were leaders, people already in contact with EUPATI CH, or expected to have an interest in PI. The interviews were done over the phone or Skype.

Data Collection

The online survey consisted of 14 questions, seven closed and seven open, on the value of PI, stakeholders' ongoing PI activities, priority areas for each stakeholder group, and their collaboration with the other stakeholders (**Appendix 2**). In particular, the survey gathered information on the mission of each organization or group, its active involvement of patients, its difficulties and achievements in collaborating with other groups, and major impediments to developing active PI. An additional question provided respondents the opportunity to give their expectations of the role EUPATI CH could or should play in PI.

The interview followed a semi-structured format with six main questions and allowed space for comments and explanations from both the interviewee and the interviewer (**Appendix 3**). The selected stakeholders received an invitation letter with information on the project, modalities of the interview, confidentiality, and anonymization of the results. The stakeholders who consented to being interviewed received the sample questions at least 2 weeks in advance of the interview. The questions focused on the PI strategy in medicines R&D of the respective stakeholder group/organization, its ongoing activities, difficulties it has faced related to PI, and its future plans for PI. There was an additional optional question on the stakeholder's opinion of EUPATI CH and his or her expectations of EUPATI CH's role in PI in Switzerland.

The interviews were recorded and transcribed verbatim, and the transcriptions were compared with the interviewer's notes. A summary of the transcription was sent to the interviewees for approval to ensure both the accuracy of the overall content of the responses and the internal validity of the results (6). The transcription text itself and the analysis of it were neither checked nor modified by the interviewees.

Data Analysis

A mixed methods approach was applied.

Answers to the online survey's closed questions were analyzed using a quantitative approach. Answers to closed questions were either on a four-level scale (very important, important, not at all, I don't know), within pre-specified categories, or yes/no and were reported as a percentage of the respondents.

For the interviews a qualitative analysis was performed using a thematic analysis approach (7). This approach involved reading the transcriptions of the interviews, underlining key phrases and phrases that evoked some reflection, and placing them in a list.

This list was used to generate codes (8). This approach allowed EUPATI CH to combine codes matching key phrases from various interviews. Codes could then be combined to derive themes, which could be related to each other. For each category of stakeholder and for each question, the main themes were identified and similar themes from different stakeholder groups were merged into main themes for each question.

The transcriptions of the interviews were analyzed separately by two persons (the interviewer and an expert in qualitative analysis), who then compared the results while referring to the specific parts of the transcription (9). A descriptive comparative analysis of themes among the various stakeholder groups was then performed to extract common and possibly relevant factors that could affect PI.

RESULTS

Online Survey

The online survey was sent to 520 stakeholders in January 2019 and was kept open for 4 weeks. The response rate was 10.5% (55/520), and the analyses were performed on a total of 39 evaluable responses. Sixteen responses were not evaluable because answers were either completely missing in 8 cases or the survey was only partially completed in eight additional cases. **Table 1** summarizes the responses to the online survey, which are described in detail in the following paragraphs.

The largest group of survey respondents were patients (45%), the majority of whom were members of EUPATI CH. They were followed by researchers from academia (25%), healthcare professionals (23%), representatives from the pharmaceutical industry (9%), and policymakers/regulators (6%).

TABLE 1 | Responses to questions in the online survey.

	Responses (%)
Stakeholder category*	
Patient organizations	45
Academic research representatives	25
Healthcare professionals	23
Pharmaceutical industry representatives	9
Policymakers and regulators	6
Current PI limited in medicines R&D	38
Barriers to PI*	
Lack of education	21
Lack of collaboration	16
Language barriers	13
Lack of support	13
Lack of funds and human resources	65
Priority areas for patients	
Training and education	60
PI in processes	63
Improving own competence in PI	70
Understanding stakeholders' responsibilities	44
Understanding stakeholders' roles	45
Skills development	40
Guidance, framework, tools	40
Best practices	46

**Multiple answers possible.*

There was almost general agreement on the meaning of PI, which was understood as active collaboration and partnership with all stakeholders while taking into account patients' needs and preferences in the elaboration of projects, the review of protocols, and the composition of advisory boards.

Some 38% of respondents judged their ongoing PI efforts to be limited or absent. A major barrier to meaningful PI in medicines R&D mentioned by respondents was a lack of funds (65%), which was almost always associated with lack of human resources. Other barriers mentioned were a lack of education and/or information on this particular topic and on how to become a patient advocate (21%), a lack of collaboration with stakeholders, in particular with academic institutions (16%), difficulty in finding suitable patients due to language barriers (13%), a lack of networking together with a lack of lobbying and support from existing structures (13%). The following impediments were also identified: PI in R&D is not the main focus of an organization, a lack of awareness of PI by key actors (hospitals, medical faculties), difficulties in reaching the experts, fear, and skepticism.

When asked to rate priorities, patients rated the following areas the highest: being involved in processes (63%), receiving training and education (60%), and understanding different stakeholders' responsibilities (44%). In addition, 70% of patient respondents would like to improve their capabilities in or knowledge of PI, in particular how to ensure reliability, stability, and interaction with patient groups, how to interact with stakeholders, and how to spread awareness of PI as a person and as a society.

TABLE 2 | Face-to-face interviews: Qualitative analysis per stakeholder group.

Stakeholder group	Contacted	Accepted interviews	Qualitative analysis
Patient organizations	8	4*	4
Academia	6	5**	5
Policymakers and regulators	3	2***	2
Pharmaceutical industry	4	3**	3
	20	14	14

**2 never replied, 1 was too busy, 1 interview was cancelled and only written text was provided by the organization.*
***1 never replied.*
****1 not allowed.*

Face-to-Face Interviews

Table 2 presents the response rates to the invitation for a face–to-face interview for each group of stakeholders. Fourteen interviews, with an average duration of 45 min (range: 30–55 min.), were conducted and analyzed. Quotes from interviewees that are used in this article are presented in italics and within quotation marks so they can be easily identified. A superscript number indicates which quote from an interviewee a specific statement corresponds to (**Appendix 4**).

Stakeholders' Patient Involvement Strategies, Ongoing Activities, and Successes

In terms of strategies—either implemented or planned—to increase PI in medicines R&D, by patient organizations reported increasing collaboration with other stakeholders as a strategy (**Table 3A**). For small patient organizations, it was very important to have a "united voice" with other patient organizations when collaborating with other stakeholders. Collaborating with the pharmaceutical industry was also an important strategy for patient organizations because it facilitated reimbursement, access to active compounds, and research on new drugs (1). Collaborating with some regulators was experienced as being difficult; however, the value of being in contact with both regulators and health authorities was generally recognized.

For some large patient organizations, collaborating with other patient organizations was not part of their main strategy because collaboration could result in heterogeneous objectives and create confusion. Some of the larger organizations do not collaborate with the pharmaceutical industry in order to maintain financial independence (2), which was also reported as one of the difficulties encountered by stakeholders in the pharmaceutical industry (**Table 3B**). The pharmaceutical industry aims to increase its collaboration with large patient organizations (either European or national) and their local affiliates in order to establish contact with patients or patient organizations and establish a long-term collaboration as equal partners.

Patient education is a very important activity for patient organizations. Education *"like EUPATI"* mainly covers the whole life cycle of a product, but some members have also requested training on how to improve their public communication skills

TABLE 3A | Qualitative analysis: Main themes for respondents from patient organizations and in academia.

	Strategies	Ongoing activities	Successes	Difficulties	Future activities
Stakeholder group (n:4)					
Patient organizations (2 small, 2 large)	• ↑ Collaboration with SKs • Educated pts: 1) Make informed decision 2) ↑ Awareness pts rights 3) Speak effectively • Direct PI (boards, events, communication, data collection)	• Data collection, scientific boards • Online strategy • Definition of objectives of future research • Organization of events	• ↑ SK awareness • Good collaboration with pharma and some SKs (clinicians, pt orgs)	• With members • Other SKs (mainly authorities and other pt orgs) • Lack of funding • ↑ Complexity of disease and treatment	• ↑ Collaboration with authorities and other pt orgs • Enable pts to become active/train to be experts • ↑ External communication activities
Stakeholder group (n:2)					
Academia	• Direct PI • ↑ PI by: 1) ↑Awareness 2) Making it a high-priority program	• PI as evaluation criteria for academic studies • Building up network of the society • Direct PI in: 1) Registry for major problems 2) Focus groups 3) Boards	Too early	• Collaboration with pts/parents: 1) How to contact them 2) How to find the proper representative 3) Lack of time 4) Little scientific knowledge: • Highly specialized studies • Small, disease-specific orgs • Trial failures due to low feasibility, pt accrual	• ↑ PI by: 1) Looking for parents interested in research 2) Direct involvement in projects 3) ↑ Funding • Develop research in the community

SK, stakeholder; pt, patient; PI, patient involvement; EC, ethics committee; WG, working group; GC, general consent; DB, database; orgs, organizations.

TABLE 3B | Qualitative analysis: Main themes for policymakers and regulators and respondents in the pharmaceutical industry.

	Strategies	Ongoing activities	Successes	Difficulties	Future activities
Stakeholder group (n:2)					
Policymakers and regulators	• Involve pts in ECs • ↑ Information for pts/laypeople	• Educational programs for new EC members • Collaboration with health leagues	• Good contact with pt orgs • ↑ pts' attention to e-health literacy	• Poor acceptance of GC • Heterogeneity of pt orgs • Reluctance of some SKs to involve pts	• List of pts to be contacted • Research on best GC • ↑ PI in e-health information
Stakeholder group (n:2)					
Pharmaceutical industry (n:3)	• Global strategy: pt-dedicated teams and local representatives • Increase: 1. Knowledge of pt advocacy 2. Pt empowerment through education 3. Equality in partnership with pts	• Involve local pt representatives • Bring pts' view into whole life cycle • Long-term teaching in collaboration with EU umbrella orgs • Use pt advocates to empower pts	• ↑ PI • Ongoing community studies • Involvement in projects of international pt orgs	• Change is too slow in industry • Collaboration with some pt organizations • Pharma industry's bad reputation	• Cover all activities in development • Increase internal PI awareness • Organize events to bring together pt orgs.

SK, stakeholder; pt, patient; PI, patient involvement; EC, ethics committee; GC, general consent; EU, European Union; orgs, organizations.

(3). Some patients would like to be more involved in discussions with authorities such as Switzerland's Federal Office of Public Health (FOPH), but they cannot because of their perceived lack of competence. Training provided by EUPATI could represent a great opportunity for patients to achieve a more active, direct role in an organization (4). Patient education is also one of the pharmaceutical industry's strategies, in particular in collaboration with EU umbrella patient organizations for long-term teaching; related activities are already underway (**Table 3B**). It is part of a global strategy to have teams dedicated to increasing

patient empowerment and integrating patients' views in all phases of the medicines life cycle.

From both academia's and patient organizations' perspectives, direct PI was reported as an important strategy in a variety of activities (e.g., the organization of events like patients' day, scientific boards, data collection, and focus groups). Specific activities varied according to the needs and mission of an organization or institution.

In the academic setting, a reported strategy for promoting PI entailed raising physicians' awareness of PI, setting PI as a high priority topic for the next 5 years, and raising patients' awareness of PI by reporting study results or research activities in social media. Patients also play a major role in the collection of personal data in prospective registries and in the evaluation of quality of life (QoL) questionnaires for the purpose of developing tools that are able to evaluate the real burden of symptoms relevant to patients (5).

Patients participate in focus groups, sometimes led by the pharmaceutical industry, and are on a variety of boards, such as scientific boards that evaluate clinical study proposals. One respondent noted, *"It's important to have people living with a disease included in research decisions on what research is funded."*

Difficulties Stakeholders Faced With Patient Involvement

All patient organizations interviewed reported difficulties interacting with the authorities, in particular with Switzerland's Federal Office of Public Health (FOPH). One patient expressed his concern about the lack of PI and the lack of control at the regulatory level on the upcoming availability of effective personalized treatments that patients do not have guaranteed access to (6). A lack of funding and human resources applies to almost all stakeholders, in particular small patient organizations. This impedes hiring additional personnel and implementing new programs and activities (7).

Difficulties working with patients occur in a variety of situations according to various stakeholder groups. For patient organizations, one difficulty is how to actively involve members because they need to be instructed on how to perform tasks and require support by a dedicated person. One patient organization reported difficulty finding patient experts willing to assess many research projects (8) and difficulty representing a more general patient perspective—a situation also observed by regulators interested in the contributions of patients who are members of ethics committees.

One academic representative mentioned that it is difficult to find parents for pediatric studies who are interested in research beyond their own children. In addition, some parents have very little knowledge of rules, regulations, and limitations, which decreases the value of their participation on boards. Despite these difficulties, stakeholders want to have patients on boards so they can share their experience, perspectives, and needs.

Pharmaceutical companies' main difficulties were improving the internal appreciation of the value of PI and overcoming an external negative reputation due to previous questionable behavior, a factor that affects collaboration with some patient organizations. For regulators, the main difficulties were the poor acceptance of general consent (GC) and the heterogeneity of patient organizations, which makes it difficult to find educated patients willing to serve as patient representatives in an ethics committee.

TABLE 4 | Qualitative analysis of main themes related to EUPATI CH: Desired activities, criticisms, and its expected role.

Desired activities
EUPATI CH should provide:
• Training for patients (pt orgs, A) and the pharmaceutical industry (P)
• Networking with other patient organizations (pt orgs, R, A)
• Information to patients (pt orgs), the community (R), and academia (A)
• A shared opinion on questions related to patients in clinical research (R)
Criticisms
• Lack of clarity regarding mission (P)
• Unfulfilled tasks (P)
• EUPATI CH's financial support from the pharmaceutical industry (R, A)
Expected role of EUPATI CH
• Connect with patient advocates (P)
• Run multi-stakeholder initiatives to support patients/the community (P, pt orgs)

pt orgs, patient organizations; P, pharmaceutical industry; A, academia; R, policymakers and regulators.

Stakeholders' Future Patient Involvement Activities

Patient organizations plan to direct some of their future activities at further improving ongoing initiatives, in particular those with authorities, as well as increasing patient education (9) *"because being active as a patient has a direct benefit for ourselves"* and developing external communication and networking (**Table 3A**).

In academia, future activities will be aimed at improving PI in research as well as improving collaboration with patient organizations. Future activities will also focus on developing a stronger link between university hospitals and the community in order to explore the possibility of addressing questions that are more important to the community than to the university hospitals (10).

For the pharmaceutical industry, future activities will be directed at involving patients in all activities of medicines development and organizing events to bring patient organizations together.

STAKEHOLDERS' COMMENTS DIRECTED AT EUPATI CH

Desired Activities

More EUPATI patient training was one the activities most desired by patient organizations, academia, and the pharmaceutical industry, as mentioned in both the online survey and the direct interviews (**Table 4**). For academia, it would also be helpful to have EUPATI training to increase interaction with EUPATI CH and the use of its toolbox material (11).

Another desired activity, also mentioned in both the online survey and the direct interviews, was support for PI promotion

and interaction among patient groups, with EUPATI *"being a good neutral platform where the patient groups get together."* For regulators, EUPATI CH can find shared opinions on questions of national relevance, for example general consent (GC) or the patient's role in ethics committees, and can bring patient information from the European level to the specific national needs of an organization (12).

Criticisms and Expected Tasks

One criticism of EUPATI CH, raised by a pharmaceutical company representative, was the lack of clarity on EUPATI CH's mission and objectives in relation to those of EUPATI at the European level that EUPATI CH strives to adapt and implement (**Table 4**). EUPATI's mission is to offer patient training and thus empower and connect patient advocates as well as scale up know-how in organizations and people. The pharmaceutical industry representative criticized EUPATI CH for not having done this yet [13].

Another criticism made by some academic respondents was the lack of transparency regarding EUPATI CH's funding. *"It's important for your credibility that you can demonstrate where the funding is coming from."* The IMI-EUPATI project was set up as a public-private partnership, whereas EUPATI CH is a private association. Nevertheless, regulators raised the concern that EUPATI CH could be partly financed by industry and thus have a potential conflict of interest [14].

DISCUSSION

EUPATI CH undertook this multi-stakeholder project in order to obtain recommendations for improving its activities related to the promotion of PI in medicines R&D in Switzerland.

For the performance of the study we applied a mixed-method design to get a more complete understanding of the phenomenon and hear the voices of Eupati CH stakeholders (12).

In the small, selected population surveyed, PI in medicines R&D was judged to be limited or absent by 38% of respondents. For patient organizations, the qualitative analysis clarified some aspects of the main impediments (lack of funds, lack of human resources and knowledge, lack of interactions with other stakeholders) which had been already reported in the quantitative analysis.

The respondents identified the main impediments to PI in medicines R&D in Switzerland as lack of funds and human resources (65%), lack of knowledge and capabilities (21%),lack of collaboration (16%). The qualitative analysis confirmed those results and further defined the characteristics of the impediments (**Tables 3A**,**B**).

There is a general agreement on the relevance of information on the value of a direct PI in clinical research and of an increased collaboration among different stakeholders. Additional points are the lack of funds and human resources. For patients organizations, there is a specific need for training to become an active expert and to increase the collaboration with other patient organizations and authorities.

One important success of EUPATI was, at least for small organizations, the possibility to collaborate with academia through direct involvement in the preparation and organization of clinical studies. This is a success because it confers a primary role to patients and leads to the improvement of clinical research and patient care. As one patient stated, *"You cannot have a successful project if you are not also taking into account patients' needs."*

Stakeholders' opinions on the opportunities and benefits of collaborating with the pharmaceutical industry were divergent and seemed to be dependent, at least partly, on the size, financial resources, and availability of an effective treatment as well as the terms of the collaboration.

The difficulties related to PI in medicines R&D that were identified in EUPATI CH's survey have also been documented in other countries. For example, a lack of funding and available time to support panel members and patient organizations, tension between various stakeholder groups when developing and conducting clinical research, and concern related to the level of patients' and the public's understanding of certain types of research were the main difficulties identified when a PPI model was implemented in cancer and palliative care in the United Kingdom (10).

The limitations of the present evaluation are the small sample size and the favorable selection of the population studied, which potentially reduces the transferability of the results. Potential reasons for the poor response to the survey were declared lack of interest, survey fatigue, lack of knowledge of EUPATI, difficulties in identifying the person responsible of patient involvement in Switzerland within large organizations The innovative aspect is the application of a qualitative analysis of stakeholders' opinions and comments, thus bringing in the voice of patients as well as public opinion in two complementary surveys: one online and one as direct interviews. This dual approach helped to clarify some of the features of the data collected in the online survey.

Recommendations for Future EUPATI CH Activities

EUPATI's competence in education and training was appreciated by all stakeholder groups. Besides education on medicines R&D, stakeholders requested that EUPATI CH teach communication skills in order to improve direct interactions between patients and regulatory bodies.

Generally, stakeholders support EUPATI CH's collaboration with pharmaceutical companies in education and training but think that it should first be discussed and clarified in terms of content, modalities, audience, scientific freedom, and the role of EUPATI CH.

Another role EUPATI CH could assume is that of a neutral national platform that fosters multi-stakeholder events, channels patient-relevant information from the European level to the national level, and facilitates networking.

The need for multi-stakeholder collaboration to improve PI in healthcare is also the conclusion of a survey conducted by EUPATI BE, a platform for patient education established in 2017 as EUPATI's National Platform in Belgium (11). Its survey was conducted on different stakeholder groups (academic stakeholders, patient organizations, patients, industry, and policymakers) than those in our study. The major barriers to PI identified in EUPATI BE's survey were a lack of information and education, the lack of a favorable regulatory and ethics

environment, a lack of PI awareness, low levels of communication and trust, and the lack of a systematic and structured approach. In all these areas, EUPATI and its national platforms could play a strategic and proactive role in the future.

Respondents' criticisms of EUPATI CH are useful for highlighting weaknesses in EUPATI CH's activities so far and for identifying activities that should be implemented in the near future. The lack of clarity regarding EUPATI CH's mission may be partly due to the limited extent and lack of clarity of information that EUPATI CH has distributed, but it could also be related to a lack of common focus in EUPATI CH's activities.

To address these criticisms, EUPATI CH needs to take a more systematic and structured approach to PI in order for its PI efforts to be efficient and effective. In addition, adequate funding, transparency, codes of conduct for all involved stakeholders, and overarching policies are needed. Another step EUPATI CH should take is to prepare clear, straightforward information on its mission, structure, and financial support as well as its relationship with pharmaceutical companies. This information can then be distributed through various platforms, communication channels, and social media. Other recommendations EUPATI CH can act on in order to fulfill its mission to improve patient empowerment are to provide more PI education and host multi-stakeholder events. With this in mind, EUPATI CH is currently preparing a training course for patients and patient representatives that aims to teach them the fundamentals of clinical research and how these fundamentals apply within the context of legal and ethical requirements in Switzerland.

From a more general perspective, an increase awareness of the community on the value and benefit of a direct involvement of patients in healthcare research should be pursued and supported by the different stakeholders to become an important component of clinical practice.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CSe was responsible for the academic design and drafted the article with CSc, AM, and DH. IK substantially revised the article and DH provided critical insight and text revision. CSe was responsible for the study design, data analysis, and data interpretation. CSc was responsible for the design and preparation of the online survey. AT and LB performed the qualitative analysis of data and interpretation. All authors read and approved the final manuscript.

FUNDING

EUPATI CH funded this study through an unrestricted grant from Amgen.

ACKNOWLEDGMENTS

We would like to thank all the stakeholders for their participation. The stakeholder analysis was done in the context of a master's thesis in pharmaceutical medicine at the European Center of Pharmaceutical Medicine (ECPM) at the University of Basel. We also wish to thank Annette Mollet and Thomas Szucs for this opportunity and for their support in the development of the thesis, Jelena Puljic for transcribing the interviews and typing the master thesis, and Valentina Rusca for typing the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.795659/full#supplementary-material

REFERENCES

1. Buck D, Gamble C, Dudley L, Preston J, Hanley B, Williamson PR, et al. From plans to actions in patient and public involvement: qualitative study of documented plans and the accounts of researchers and patients sampled from a cohort of clinical trials. *BMJ Open.* (2014) 4:e006400. doi: 10.1136/bmjopen-2014-006400
2. Stewart R, Liabo K. Involvement in research without compromising research quality. *J Health Serv Res Policy.* (2012) 17:248–51. doi: 10.1258/jhsrp.2012.011086
3. EUPATI. Available online at: https://www.eupati.eu/closing-report-eupati-2012-2017/ (accessed December 31, 2017).
4. Deverka PA, Lavallee DC, Desai PJ, Esmail LC, Ramsey SD, Veenstra DL, et al. Stakeholder participation in comparative effectiveness research: defining a framework for effective engagement. *J Comp Eff Res.* (2012) 1:181–94. doi: 10.2217/cer.12.7
5. Morse JM. Critical analysis of strategies for determining rigor in qualitative inquiry. *Qual Health Res.* (2015) 25:1212–22. doi: 10.1177/1049732315588501
6. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med.* (2014) 89:1245–51. doi: 10.1097/ACM.0000000000000388
7. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res in Psychol.* (2006) 3:77–101. doi: 10.1191/1478088706qp063oa
8. McIntosh MJ, Morse JM. Situating and constructing diversity in semi structured interviews. *Glob Qualit Nurses Res.* (2015) 2:1–12. doi: 10.1177/2333393615597674
9. Holloway I, Wheeler S. *Qualitative Research in Nursing and Healthcare*. Hoboken, NJ: Blackwell Publishing Ltd. (2010).
10. Collins K, Boote J, Ardron D, Gath J, Green T, Ahmedzai SH, et al. Making patient and public involvement in cancer and palliative care research a

reality: academic support is vital for success. *BMJ Supp Pall Care.* (2015) 5:203–6. doi: 10.1136/bmjspcare-2014-000750
11. Grine L, Janssens R, van Overbeeke E, Derijcke D, Silva M, Delys B, et al. Improving patient involvement in the lifecycle of medicines: insights from the EUPATI BE survey. *Front Med.* (2020) 7:36. doi: 10.3389/fmed.2020.00036
12. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. *Health Serv Res.* (2013) 48(6 Pt 2):2134–56. doi: 10.1111/1475-6773.12117

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Medicine

PERSPECTIVE
published: 10 January 2022
doi: 10.3389/fmed.2021.817663

Repurposing of Medicines in the EU: Launch of a Pilot Framework

Charlotte Asker-Hagelberg[1†], Tomas Boran[2†], Christelle Bouygues[3†], Sini Marika Eskola[4†], Laszlo Helmle[5†], César Hernández[6†], François Houÿez[7†], Helen Lee[8†], Dimitra D. Lingri[9†], Laurent Louette[10†], Lydie Meheus[11†], Wim Penninckx[12†] and Beata Stepniewska[13†]*

[1] Swedish Medical Products Agency, Uppsala, Sweden, [2] Director of the Marketing Authorisation Section, State Institute for Drug Control (SUKL), Prague, Czechia, [3] Regulatory Affairs Office, Human Medicines Division, European Medicines Agency (EMA), Amsterdam, Netherlands, [4] European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, Belgium, [5] European Commission Directorate-General Research and Innovation, Brussels, Belgium, [6] Alternate Representative of Spain in EMA Management Board, Spanish Agency of Medicines and Medical Devices (AEMPS), Madrid, Spain, [7] Treatment Information and Access, European Organisation for Rare Diseases (Eurordis), Paris, France, [8] European Commission Directorate-General for Health and Food Safety, Brussels, Belgium, [9] Association Internationale de la Mutualité Pharmaceutical Working Group, Brussels, Belgium, [10] European Confederation of Pharmaceutical Entrepreneurs, Brussels, Belgium, [11] Anticancer Fund, Appointed Alternate of the Committee for Advanced Therapies of the European Medicines Agency (CAT/EMA) to Represent Patients, Strombeek-Bever, Belgium, [12] Federal Agency of Medicines and Health Products (FAMHP), Brussels, Belgium, [13] Medicines for Europe, Brussels, Belgium

OPEN ACCESS

Edited by:
Steffen Thirstrup, NDA Advisory Services ltd, United Kingdom

Reviewed by:
Frits Lekkerkerker, Consultant, Amsterdam, Netherlands

***Correspondence:**
César Hernández
chernandezg@aemps.es

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *18 November 2021*
Accepted: *14 December 2021*
Published: *10 January 2022*

Citation:
Asker-Hagelberg C, Boran T, Bouygues C, Eskola SM, Helmle L, Hernández C, Houÿez F, Lee H, Lingri DD, Louette L, Meheus L, Penninckx W and Stepniewska B (2022) Repurposing of Medicines in the EU: Launch of a Pilot Framework. Front. Med. 8:817663. doi: 10.3389/fmed.2021.817663

Repurposing of authorised medicines has been under discussion for a long time. Drug repurposing is the process of identifying a new use for an existing medicine in an indication outside the scope of the original approved indication. Indeed, the COVID-19 health crisis has brought the concept to the frontline by proving the usefulness of this practise in favour of patients for an early access to treatment. Under the umbrella of the Pharmaceutical Committee and as a result of the discussions at the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) a virtual Repurposing Observatory Group (RepOG) was set up in 2019 to define and test the practical aspects of a pilot project thought to provide support to "not-for-profit" stakeholders generating or gathering data for a new therapeutic use for an authorised medicine. The group's initial plan was impacted by the outbreak of the SARS-CoV-2 pandemic and the launch of the pilot needed to be postponed. This article describes the progress and the activities conducted by the group during this past and yet extraordinary 2020–2021 to keep the project alive and explores on the background of this topic together with the obvious opportunities this health crisis has brought up in terms of repurposing of medicines.

Keywords: repurposing, off patent authorised medicines, COVID-19, patient access, European Union, repurposing observatory group, pilot launch

INTRODUCTION

Medicine repurposing is the process of identifying and substantiating a new use for an existing medicine/active substance outside the scope of the original indications (1–3) as well as the process of allowing a medicinal product to broaden its position in a relevant market (excluding the extension of an authorised indication to those of a new age group or to another genetic mutation). It includes new therapeutic uses for existing medicines, different formulations of the same medicine, and/or creating new combinations of medicines or medicines with medical devices. Repurposing of medicines is part of the routine research portfolio of both the pharmaceutical industry and

academic institutions in the search for solutions for those conditions with unmet medical needs (4, 5) including aspects related to sustainability and patient access.

The perspective for repurposing is quite different when one considers finding a new use for (i) an active substance that has never been authorised (ii) a medicine that is still within intellectual property[1] or regulatory data protection (6) or (iii) a well-known medicine that is out of any protection period. While pharmaceutical companies may find a commercial interest in pursuing a non-clinical and clinical development in the first two cases, they are less likely to carry out such development for out-of-protection medicines (7–10). In the third case, the current environment (regulatory and market access) does not encourage pharmaceutical companies to further explore existing opportunities in repurposing. A direct consequence is that pharmaceutical companies usually explore repurposing medicines that are still within the period of regulatory data protection. Other parties, including academic institutions and learned societies, are more willing in general to explore repurposing options when medicines are out of these protection periods (11). However, this academic research rarely has an impact in terms of regulatory recognition of a new use and indication. Academic sponsors usually do not intend to become marketing authorisation holders, and may have limited knowledge about regulatory requirements. In support, the EU Commission has initiated a regulatory science curriculum project called STARS[2] (Strengthening Training of Academia in Regulatory Science) (12, 13). In addition, the current regulatory pathways do not foresee submission of data by parties that are not intending to be a marketing authorisation holder. This can mean that medicines are used outside their authorised uses (off-label) and official clinical guidelines might recommend their use based on available evidence, despite not being formally authorised (14, 15).

REGULATORY CONTEXT AND PROPOSED WAY FORWARD

There is a need to find a way for new and promising indications that will benefit patients in all EU member states in fulfilling an unmet medical need to be included on-label. Not converting off-label use into on-label use has a number of negative consequences. First of all, this means that this use is not included in the regulatory documents (i.e., summary of product characteristics and patient information leaflet). Hence, patients are not informed about the appropriate conditions of the particular use and warnings in the patient information leaflet. Patient access to potentially effective treatments may also be hampered in the absence of a formal authorisation. Moreover, when patients cannot lean on written and assessed information about the use it may lead to distrust or a sense of insecurity in the treatment. It may also have reimbursement impacts in some countries, but not in others (16). Secondly, established medicines that are no longer standard of care may also be withdrawn from the market without the full awareness of the potential off-label uses and patient needs, as these are not officially included in the label. Finally, repurposing of well-known, established medicines into new, sometimes higher priced medicines invariably introduces tension in the health systems that play against access. In other cases of investing in repurposing and adding a new indication to medicines' label, this effort is not recognised by market access mechanisms and prices remains the same as for other similar products without repurposed indication. It has therefore been recommended to find solutions to facilitate bringing new uses for medicines "on-label" by developing a collaborative framework between not-for-profit and academic organisations, patients organisations, pharmaceutical industry, health technology assessment bodies, payers, and regulators (17).

Within this context, a multistakeholder subgroup of the European Commission's Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) started discussing a proposal to develop a framework for the repurposing of established medicines in the European Union. This group was made up of representatives of the European Commission, the European Medicines Agency (EMA), and National Competent Authorities (NCA) of several Member States as well as representatives of patients associations, research organisations and pharmaceutical industry associations and payers. On 11 July 2019, the Pharmaceutical Committee endorsed the proposal (18) of a framework to provide visible support to "not-for-profit" stakeholders, termed "champions," who are generating or gathering data in accordance with regulatory standards for a new therapeutic use for an authorised active substance or medicine. The framework is only intended for medicines already out of intellectual property, data or marketing protection. The "champion" would typically be a "not-for-profit" organisation, for example an entity or a person from a charity or patient group, academic unit, learned society, research funder or payer. The framework builds on existing regulatory tools, namely support from the EU-Innovation Network (EU-IN) and scientific and/or regulatory advice provided through EMA and/or a NCA to provide guidance to the champion. The framework foresees that the champion would in time liaise with the marketing authorisation holder (MAH) of the potentially repurposed medicine, with the expectation that the latter can initiate an application for the new indication of use (i.e., on-label use) of the medicine by applying for variation, line extension or new marketing authorisation to a regulatory authority.

The next step is to establish a pilot to test the core components of the framework. This exercise would explore, among other aspects, the feasibility of producing and/or gathering by the "champions" of the required information for the regulatory approval, the adequacy of the current regulatory pathways as well as the suitability of current regulatory tools for the repurposing, and/or the challenges of the current systems for providing incentives to champions and MAHs to participate in the repurposing framework. **Figure 1** gives an overview of the process of the pilot project.

[1]As per the World Intellectual Property Organisation (WIPO): Intellectual property (IP) refers to creations of the mind –everything from works of art to inventions, computer programs to trademarks and other commercial signs.
[2]https://www.csa-stars.eu/

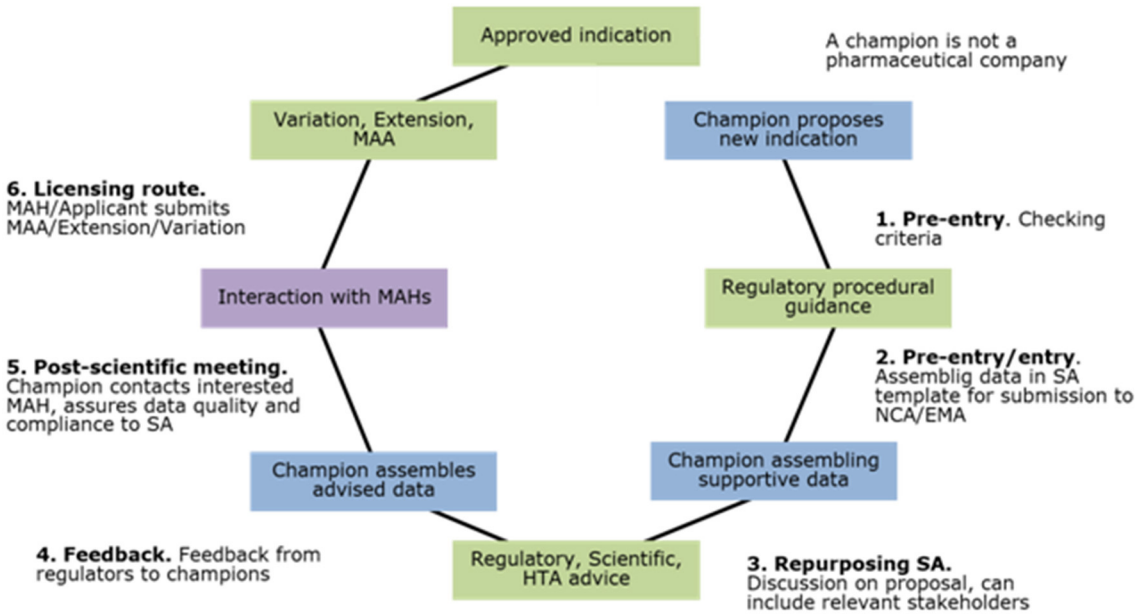


FIGURE 1 | Regulatory framework for the repurposing of medicinal products out of data and patent protection by not-for-profit-organisations.

For these purposes, a Repurposing Observatory Group (RepOG)[3] was established in July 2019 with the aim of defining the practical aspects of the implementation of the pilot phase and to report on the success and opportunities of the project. The RepOG initiated its activities by further developing the framework: (i) establishing contact points and the steps for involvement of EMA's scientific advice working party (SAWP) and the EU-IN, (ii) developing materials such as a template for "champions" seeking scientific advice, (iii) a Question & Answer document, and (iv) a dissemination plan targeting potential "champions" as well as MAH with medicines that may be, at some point, be subject to the repurposing framework.

DISCUSSION

March 2020 was the planned date for launching the pilot in the EU. The commitment of the regulatory system was demonstrated by: the involvement of several NCAs and EMA via the EU-IN and the inclusion of the repurposing pilot in the EU-IN annual workplan; the inclusion of proposed actions to support repurposing in the EMA regulatory science strategy; and EMA's recent announcement that protocol assistance for academic organisations developing orphan medicines will now be free of charge (19). It can also be noted that EMA adapted the policy on conflicts of interest for patients/experts who would engage in drug repurposing or whose organisation would and which entered into force on 1 January 2021.

Unfortunately, we all know now that March 2020 is not going to be remembered because of the launch of a pilot project for repurposing. March 2020 will be kept in our minds because the SARS-CoV-2 virus causing a disease named COVID-19 struck our health systems, our societies and our citizens unlike anything else in the last 65 or more years. The EU and global medicines agencies had to reorganise themselves to tackle the health crisis and some ongoing activities were temporarily suspended or delayed. Among them, the launch of the repurposing pilot, the finalisation of materials to raise awareness of the repurposing project, and the regular meetings with stakeholders were postponed.

While the initial launch plans were interrupted by the COVID-19 pandemic, to some extent the pilot has started by itself. The health crisis has highlighted the massive opportunities for repurposing, acting as a kind of accelerator. This has become evident as knowledge and hypotheses about COVID-19 have emerged rapidly. EMA and the NCAs have been approached by sponsors in health care for central and national scientific advice on clinical trials in possible repurposing projects. In August 2020 there were more than 300 substances and 1,000 clinical trials recorded in a database produced by the Anticancer Fund[4] (20). Moreover, in February 2021 there were around 1,600 drugs by over 1,000 sponsors in clinical trials recorded in a database by Informa Pharma Intelligence[5] It is clear that repurposing of

[3]RepOG composition at the time of the paper elaboration: Anticancer Fund (ACF), Association Internationale de la Mutualité (AIM), Federal Agency of Medicines and Health Products, Belgium (FAMHP), European Organisation for Rare Diseases (EURORDIS), European Federation of Pharmaceutical Industries and Associations (EFPIA), European Medicines Agency (EMA), European Commission (EC), European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), Medicines for Europe, Spanish Agency of Medicines and Medical Devices (AEMPS), State Institute For Drug Control (SUKL), Swedish Medical Products Agency (MPA).

[4]Covid19db | ReDO Project (redo-project.org).

[5]https://dataanalytics.citeline.com/coronavirus/

well-known medicines for COVID-19 disease is done extensively. Outside the scope of COVID-19, repurposing also seems to have taken off (21–23).

First, it has shown the various angles of repurposing, from medicines that have never been approved before but have been the subject of clinical development in other indications (like remdesivir), medicines approved but still within protection periods (e.g., tocilizumab, sarilumab or baricitinib, among others) to medicines out of protection periods (e.g., hydroxychloroquine, lopinavir, interferon or dexamethasone, among others).

Secondly, it has shown the different perspectives from where clinical proof or evidence may come. In fact, before the COVID-19 crisis, roughly 80% of the clinical trials approved were sponsored by pharmaceutical companies and only 20% by academic sponsors. During this crisis, these numbers were more or less reversed. Furthermore, the collaboration between public and private partners has also been remarkable, with pharmaceutical companies donating their medicines to ensure the fastest possible generation of evidence. Without doubt, saturation of health systems did not create the easiest environment for clinical research and clinical trials had to be designed and be adapted pragmatically to that situation. This has prompted a debate on the suitability of such clinical trials to offer meaningful pieces of evidence. However, the contribution of experiences in clinical trials such as the RECOVERY (24), comparing the use of dexamethasone or the usual care in hospitalised COVID-19 patients, SOLIDARITY (25), comparing the use of four repurposed antiviral drugs (remdesivir, hydroxychloroquine, lopinavir or interferon beta 1a) and the standard of care in hospitalised COVID-19 patients- and REMAP-CAP[6] platform trial comparing multiple treatments for community-acquired pneumonia—should be highlighted and constitute an incredibly useful piece of evidence that complement others. These three examples of clinical trials are platform trials which compare head-to-head multiple treatments and where a "champion" acts as the sponsor.

Finally, it is also important to note that some of these results have prompted a timely recognition of a repurposed use. In July 2020, EMA initiated—at the request of the EMA Executive Director—a review (26) by the Committee for Medicinal Products for Human Use (CHMP) of the dexamethasone results from the RECOVERY trial. The CHMP issued an opinion recommending conditions for the safe and effective use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy. What is important is that, in view of the emergency situation, the CHMP exceptionally defined in its recommendation the conditions of use of dexamethasone in COVID-19 patients. Companies marketing dexamethasone medicines that wished to request this new use to be added to their product's licence could then base their request on the CHMP recommendation when submitting an application to national medicines agencies or to EMA (27). Whilst this mechanism was used in the context of an emergency situation, the importance of a scientific dialogue between partners and authorities for repurposing projects is pivotal. This is intended to be developed in the context of dedicated Scientific Advices as part of the pilot project.

[6]https://www.remapcap.org-adaptative

CONCLUSION

The subsequent waves of the COVID-19 pandemic have once again delayed the launch of this project, however, the RepOG has resumed its activities and a proposal for a new date was agreed, the pilot project has finally been launched on the 28th of October (28). In addition to COVID-19 acting as an accelerator, repurposing is also described in the Pharmaceutical Strategy for Europe (29). Moreover, the proposal is also complementary with other important ongoing initiatives like the EU-IN workplan or the STARS project. Finding a smooth way for repurposing provides many opportunities for patients, health care professionals, cooperative and payers groups, and research institutions as well as for MAHs working in the innovation or generic/biosimilar side.

We recommend everyone to stay tuned.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analysed in this study. This data can be found here: https://ec.europa.eu/health/documents/pharmaceutical-committee/stamp_en~https://www.ema.europa.eu/en/news/repurposing-authorised-medicines-pilot-support-not-profit-organisations-academia.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

REFERENCES

1. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. *Nat Rev Drug Discov*. (2004) 3:673–83. doi: 10.1038/nrd1468
2. Langedijk J, Mantel-Teeuwisse AK, Slijkerman DS, Schutjens MH. Drug repositioning and repurposing: terminology and definitions in literature. *Drug Discov Today*. (2015) 20:1027–34. doi: 10.1016/j.drudis.2015.05.001
3. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, et al. Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov*. (2019) 18:41–58. doi: 10.1038/nrd.2018.168
4. Cha Y, Erez T, Reynolds IJ, Kumar D, Ross J, Koytiger G, et al. Drug repurposing from the perspective of pharmaceutical companies. *Br J Pharmacol*. (2018) 175:168–80. doi: 10.1111/bph.13798

5. Frail DE, Brady M, Escott KJ, Holt A, Sanganee HJ, Pangalos MN, et al. Pioneering government-sponsored drug repositioning collaborations: progress and learning. *Nat Rev Drug Discov.* (2015) 14:833–41. doi: 10.1038/nrd4707
6. *Article 14(11) of Regulation (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND 242 OF THE COUNCIL of 31 March 2004 Laying Down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency. Official Journal of the European Union*. Available online at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R0726&from=EN (accessed Dec 10, 2021).
7. Breckenridge A, Jacob R. Overcoming the legal and regulatory barriers to drug repurposing. *Nat Rev Drug Discov.* (2019) 18:1–2. doi: 10.1038/nrd.2018.92
8. Hernandez JJ, Pryszlak M, Smith L, Yanchus C, Kurji N, Shahani VM, et al. Giving drugs a second chance: overcoming regulatory and financial hurdles in repurposing approved drugs as cancer therapeutics. *Front Oncol.* (2017) 7:273. doi: 10.3389/fonc.2017.00273
9. Langedijk J, Whitehead CJ, Slijkerman DS, Leufkens HG, Schutjens MH, Mantel-Teeuwisse AK. Extensions of indication throughout the drug product lifecycle: a quantitative analysis. *Drug Discov Today.* (2016) 21:348–55. doi: 10.1016/j.drudis.2015.11.009
10. Sahragardjoonegani B, Beall RF, Kesselheim AS, Hollis A. Repurposing existing drugs for new uses: a cohort study of the frequency of FDA-granted new indication exclusivities since 1997. *J Pharm Policy Pract.* (2021) 14:3. doi: 10.1186/s40545-020-00282-8
11. Davies EH, Fulton E, Brook D, Hughes DA. Affordable orphan drugs: a role for not-for-profit organizations. *Br J Clin Pharmacol.* (2017) 83:1595–1601. doi: 10.1111/bcp.13240
12. Starokozhko V, Kallio M, Kumlin Howell Å, Mäkinen Salmi A, Andrew-Nielsen G, Goldammer M, et al. Strengthening regulatory science in academia: STARS, an EU initiative to bridge the translational gap. *Drug Discov Today.* (2020) 26:283–8. doi: 10.1016/j.drudis.2020.10.017
13. Gonzalez-Quevedo R, Ziogas C, Silva I, Vegter R, Humphreys A. Advancing development of medicines by academia and non-profit research organizations in the European Union. *Nat Rev Drug Discov.* (2020) 20:245–6. doi: 10.1038/d41573-020-00205-x
14. Bugani G, Ponticelli F, Giannini F, Gallo F, Gaudenzi E, Laricchia A, et al. Practical guide to prevention of contrast-induced acute kidney injury after percutaneous coronary intervention. *Catheter Cardiovasc Interv.* (2021) 97:443–50. doi: 10.1002/ccd.28740
15. Telmesani Moss A, Chetrit M. *Colchicine in Acute Pericarditis. American College of Cardiology*. Available online at: https://www.acc.org/latest-in-cardiology/articles/2019/12/04/08/22/the-use-of-colchicine-in-pericardial-diseases (accessed October 05, 2019).
16. *Study on Off-Label Use of Medicinal Products in the European Union*. (2017). Available online at: https://ec.europa.eu/health/sites/default/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf (accessed Dec 10, 2021).
17. Verbaanderd C, Rooman I, Meheus L, Huys I. On-label or off-label? Overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients. *Front Pharmacol.* (2020) 10:1664. doi: 10.3389/fphar.2019.01664
18. *Proposal for a Framework to Support Not-For-Profit Organizations and Academia (institutions and individuals) in Drug Repurposing. Prepared by a Working Group of the Safe and Timely Access to Medicines for Patients (STAMP) Expert Group*. (2019). Available online at: https://ec.europa.eu/health/sites/health/files/files/committee/pharm773_repurposing_annex_en.pdf (accessed Dec 10, 2021).
19. *Academia Developing Medicines for Rare Diseases to Receive Free EMA Scientific Advice*. Available online at: https://www.ema.europa.eu/en/news/academia-developing-medicines-rare-diseases-receive-free-ema-scientific-advice (accessed June 23, 2020.
20. Pantziarka. P, Vandeborne.L, Meheus. L,Bouche.G. Covid19db – An online database of trials of medicinal products to prevent or treat COVID-19, with a specific focus on drug repurposing. (2020). *[Preprint]*. doi: 10.1101/2020.05.27.20114371
21. Polamreddy P, Gattu N. The drug repurposing landscape from 2012 to 2017: evolution, challenges, and possible solutions. *Drug Discov Today.* (2019) 24:789–95. doi: 10.1016/j.drudis.2018.11.022
22. Parvathaneni V, Kulkarni NS, Muth A, Gupta V. Drug repurposing: a promising tool to accelerate the drug discovery process. *Drug Discov Today.* (2019) 24:2076–85. doi: 10.1016/j.drudis.2019.06.014
23. Pantziarka P, Pirmohamed M, Mirza N. New uses for old drugs. *BMJ.* (2018) 361:k2701. doi: 10.1136/bmj.k2701
24. Recovery Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med.* (2021) 384:693–704. doi: 10.1056/NEJMoa2021436
25. Who Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, et al. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. *N Engl J Med.* (2021) 384:497–511. doi: 10.1056/NEJMoa2023184
26. *EMA Starts Review of Dexamethasone for Treating Adults With COVID-19 Requiring Respiratory Support*. Available online at: https://www.ema.europa.eu/en/news/ema-starts-review-dexamethasone-treating-adults-covid-19-requiring-respiratory-support (accessed July 24, 2020).
27. *Outcome of Art 5(3) Procedure - Product Information*. Available online at: https://www.ema.europa.eu/en/documents/other/dexamethasone-covid19-article-53-procedure-proposals-product-information_en.pdf (accessed Dec 10, 2021).
28. *Repurposing of Authorised Medicines: Pilot to Support Not-For-Profit Organisations and Academia*. Available online at: https://www.ema.europa.eu/en/news/repurposing-authorised-medicines-pilot-support-not-profit-organisations-academia (accessed October 28, 2021).
29. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. *Pharmaceutical Strategy for Europe*. (2020). Available online at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN (accessed November 25, 2020).

Author Disclaimer: The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organisations with which the author(s) is/are employed/affiliated.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Medicine

ORIGINAL RESEARCH
published: 13 January 2022
doi: 10.3389/fmed.2021.817678

ERANET JTC 2011: Submission and Activation of an International Academic Translational Project in Advanced Breast Cancer. Experience From the ET-FES Study

Manuela Monti[1], Tom Degenhardt[2], Etienne Brain[3], Rachel Wuerstlein[2], Alessandra Argusti[4], Matteo Puntoni[4], Gian Andrea Rollandi[4], Davide Corradengo[4], Luca Boni[5], Harun Ilhan[6], Oriana Nanni[1], Javier Cortes[7], Alejandro Piris-Gimenez[7], Arnoldo Piccardo[8], Massimiliano Iacozzi[8], Federica Matteucci[1], Valentina Di Iorio[1], Jean Louis Alberini[9], Carolien Schröder[10], Nadia Harbeck[2] and Alessandra Gennari[11]*

[1] *Unit of Biostatistics and Clinical Trials, Istituto di Ricovero e Cura a Carattere Scienteifico Istituto Romagnolo per lo Studio dei Tumori "DinoAmadori", Meldola, Italy,* [2] *Breast Center, Department of Obstetrics and Gynaecology, Ludwig Maximilians University Hospital of Munich, Munich, Germany,* [3] *Department of Clinical Research and Medical Oncology, Institut Curie-Hopital "René Huguenin", Saint-Cloud, France,* [4] *Clinical Trial Research Unit, Ente Ospedaliero Galliera Hospital, Genoa, Italy,* [5] *Clinical Trials Unit, Istituto Nazionale per la Ricerca sul Cancro Istituto Scientifico Tumori, Genoa, Italy,* [6] *Die Radiologie (Centre for Radiology, Nuclear Medicine and Radiotherapy), Munich, Germany,* [7] *Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain,* [8] *Department of Nuclear Medicine, Ente Ospedaliero Galliera Hospitals, Genoa, Italy,* [9] *Nuclear Medicine Department, Centre "Georges-François Leclerc", Dijon, France,* [10] *Department of Medical Oncology, Dutch Cancer Institute Nederlands Kanker Instituut - Antoni Van Leeuwenhoek, Amsterdam, Netherlands,* [11] *Department of Translational Oncology, University of Eastern Piedmont, Novara, Italy*

OPEN ACCESS

Edited by:
Sandor Kerpel-Fronius, Semmelweis University, Hungary

Reviewed by:
Lawrence Liberti, Temple University, United States
Domenico Criscuolo, Italian Society of Pharmaceutical Medicine, Italy

****Correspondence:***
Manuela Monti
manuela.monti@irst.emr.it

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *18 November 2021*
Accepted: *22 December 2021*
Published: *13 January 2022*

Citation:
Monti M, Degenhardt T, Brain E, Wuerstlein R, Argusti A, Puntoni M, Rollandi GA, Corradengo D, Boni L, Ilhan H, Nanni O, Cortes J, Piris-Gimenez A, Piccardo A, Iacozzi M, Matteucci F, Di Iorio V, Alberini JL, Schröder C, Harbeck N and Gennari A (2022) ERANET JTC 2011: Submission and Activation of an International Academic Translational Project in Advanced Breast Cancer. Experience From the ET-FES Study. Front. Med. 8:817678. doi: 10.3389/fmed.2021.817678

Background: Academic research is important to face unmet medical needs. The Oncological community encounters many hurdles in setting up multicenter investigator-driven trials mainly due to administrative complexity. The purpose of a network organization at a multinational level is to facilitate clinical trials through standardization, coordination, and education for drug development and regulatory approval.

Methods: The application of an European grant foresees the creation of a consortium which aims at facilitating multi-center academic clinical trials.

Results: The ERA-NET TRANSCAN Call 2011 on "Validation of biomarkers for personalized cancer medicine" was released on December 2011. This project included Italian, Spanish, French and German centers. The approval process included Consortium constitution, project submission, Clinical Trial Submission, and activation on a national level. The different timescales for submitting study documents in each Country and the misalignment of objections by each Competent Authority CA, generated several requests for changes to the study documents which meant amendments had to be made; as requested by the 2001/20/EC Directive, the alignment of core documents is mandatory. This procedure impacted significantly on study activation timelines. Time to first patient in was 14, 10, 28, and 31 months from the date of submission in Italy, France, Spain, and Germany, respectively. Accrual was stopped on 22nd January 2021 due to an 18F FES shortage as the primary reason but also for having exceeded the project deadlines with consequent exhaustion of the funds allocated for the project.

Conclusions: Pharmaceutical companies might be reluctant to fund research projects aimed at treatment individualization if the approval for a wider indication has already been achieved. Academic trials therefore become fundamental for promoting trials which are not attractive to big pharma. It was very difficult and time consuming to activate an academic clinical trial, for this reason, a study may become "old" as new drugs entered into the market. National institutions should promote the development of clinical research infrastructures and network with competence in regulatory, ethical, and legal skills to speed up academic research.

Keywords: ERANET, academic, regulatory in Europe, radiopharmaceuticals, PET

INTRODUCTION

Trials to improve the knowledge on personalized therapy strategies are usually developed on large-scale populations. Therefore, funding is a difficult issue, as the unmet medical needs to better understand who is really benefiting from a drug with a broad indication, does not necessarily arouse the interest of the industry (1). As a consequence, there is an unmet medical need that could be addressed by independent academic research in particular multi-institutional, international translational research. It is of great interest to strengthen translational cancer research with the integration of basic, epidemiological, preclinical, and clinical research with the implementation and evaluation of interventions in prevention, diagnosis, prognosis, treatment, and care. Oncological clinical research community encounters many hurdles in setting up multicentre trials, particularly for Investigator-driven academic trial. The main issues concern the administrative complexity and heterogeneous clinical staff training and infrastructure support that often limit the opportunity to participate into international clinical trials. Efficient planning and performance of clinical research rely on the interplay among teams of different clinicians and other components such as ethical committees, national and local authorities, promoter and drug manufactories, patient association, as well as hospital administration. Joining forces within multinational project applications and more interdisciplinary projects will be necessary to realize the full potential of the increasing number of developments for theragnostic applications. The scope of a network organization at a national level is to facilitate the effective use of molecular imaging in clinical trials through standardization, coordination, and education for drug development and regulatory approval. The Italian network model could be transferred to an European level to facilitate the participation of all network centers into Investigator-driven non-academic International multicentre clinical trials. Molecular imaging with PET is a rapidly emerging technique. In breast cancer patients, more than 45 different PET tracers have been or are presently being tested. But regretfully so far, only [^{18}F]-FDG PET has been incorporated into breast cancer guidelines. PET tracers will likely allow better breast cancer patient selection for the right treatment. However, for proof of the clinical relevance of the tracers, especially for analysis in a multicenter setting, standardization of the technology and access to the novel PET tracer are required. Funding for such an approach has largely been lacking. The ERA-NET TRANSCAN call aims at combining translational cancer research funding programs in 19 Member States and Associated Countries. TRANSCAN will concentrate translational research resources and will provide relevant financial support to address large scale problems that will be relevant for the improvement of translational cancer research in every Member State and possibly overall in Europe. TRANSCAN will identify opportunities for coordinated translational research, and will thus contribute to the development of a coordinated funding research policy shared by European countries. The activation of an international, non-profit clinical trial supported by the ERA-NET (Aligning national/regional translational cancer research programmes and activities) and funded by the European Commission requires specific timelines according to the EU rules. This paper describes the complexity of activating an international study within the ET-FES TRANSCAN project in 4 EU countries (France, Germany, Italy, and Spain).

MATERIALS AND METHODS

Project Selection for Funding According to the Type of Call

The call ERA-NET on Translational Cancer Research (TRANSCAN) First Joint Transnational Call for Proposals (JTC 2011) on: "Validation of biomarkers for personalized cancer medicine" was available for a proposal submission on 10th of January 2012. The Chief Investigator (Italian PI) decided to submit a proposal on an interventional clinical trial for breast cancer patients: Early prediction of efficacy of endocrine therapy in breast cancer: pilot study and validation with [^{18}F]-fluoroestradiol (FES) PET/CT - ET FES study. The availability of this non-invasive functional test to assess the endocrine responsiveness in the individual patient with multiple breast cancer metastasic sites represents an interesting option. The availability of new techniques such as molecular imaging with [^{18}F]-FES CT/PET offers the opportunity to improve the ability to predict the probability of response to endocrine therapy. To be compliant with the call, a consortium was created with the purpose of implementing a network of clinical centers, each including Medical Oncology Unit and Nuclear Medicine Unit

in order to optimize the multidisciplinary approach needed to perform this clinical trial for what concerned the clinical aspects, regulatory framework, logistic and technical aspects. The project coordinator implemented standard operating procedures (SOPs) and transferred them to the other participant partners, to set up an international EU network for this translational imaging project. While applications were submitted jointly by the coordinator of this group at an EU level, each Country was funded by the responsible national funding organization; funding was available by each national/regional funding organization according to their specific regulations. The funding rate within the call ranged up to a maximum of 100% of the funds requested, according to national/regional rules. Funding was granted for a maximum of 3 years according to national regulations. Applicants contacted their national/regional funding organizations prior to submitting a proposal to verify their eligibility, the eligible costs, and the potential budget available. Depending on the time needed for the administration of granting funds to the respective national/regional research groups, individual projects of a research consortium were expected to start between March and April 2013. Only if selected for funding, the project coordinator/promoter of the study, could have started the submission process of the clinical study in all Countries involved in the consortium taking into account that the clinical trial authorization process is on a national basis.

Ethics Approval Statement

Ethical approval was obtained from IRST and Romagna Ethics Committee (CEIIAV) on 22nd January 2014 (Prot. 426/I.5/242). It was conducted in accordance with the 1964 Helsinki Declaration and its later amendments and with Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all individual participants included in the study.

RESULTS

Approval Process for the European Project (Consortium Constitution and Project Submission for EU Approval)

The ERA-NET on Translational Cancer Research (TRANSCAN) Joint Transnational Call 2011 (JTC 2011) for European Research Projects on "Validation of biomarkers for personalized cancer medicine" was released in December 2011. In order to meet the call requirements, this study had to be international, so it was decided to include Spain, France and Germany. The Project Coordinator (PI) contacted the reference Nuclear Medicine Departments of each state and presented the project to them. The PI also looked for a Company authorized to produce the experimental radiopharmaceutical [^{18}F]-FES. These relations made it possible to set up the project and prepare the documentation for submission to the European call.

Consortium Constitution

The Consortium provided high competence and expertise related to the project's scope for what concerned scientific, technological and regulatory areas. In particular, it consisted of five partners from four European countries and represented in all key actors in a balanced way, in a trustworthy domain and addressed the project's key topics. A collaborative network was newly established among the Nuclear Medicine physicians, sharing all aspects related to the [^{18}F]-FES with particular emphasis on logistical and technical aspects. The Project Coordinator and Sponsor was E.O. Ospedali Galliera, Genoa, Italy; the other partners were Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, IRST IRCCS (Italy), Vall d'Hebron Insititute of Oncology (VHIO, Spain), Breast Center, Dept. OB&GYN, LMU University Hospital, Munich (Germany) and Institut Curie—Hôpital René Huguenin, Department of Medical Oncology (France). All these partners are medical Institutions of excellence, particularly dedicated to biomedical and health system research with its focus on cancer. Advanced Accelerator Applications (AAA), a French radiopharmaceutical company operating in the diagnostics and therapy field of Nuclear Medicine, located in the Technology Park (Ain, Saint GenisPouilly) was also part of the consortium and developed [^{18}F]-FES for the ET-FES TRANSCAN project.

Project Submission

After the letter of intent had been approved, the final ET-FES application was uploaded on 2nd July 2012. The proposal was approved for funding by email on 11th October 2012 by the ERANET Committee and TRANSCAN Secretariat. No additional information on the Scientific Evaluation Committee's judgments or extent of funding overall and in the different countries was provided. The Secretariat suggested that all principal investigators contacted their respective national funding organization in order to start the (national) negotiation process. The official starting date for the project was the 30th of June 2013, 8 months after the expected date. This was due to the extensive and time consuming negotiations between E.O Ospedali Galliera (Project Coordinator, PC), the Italian Ministry of Health and Liguria region as legal regional representative. In October 2013 the PC/Sponsor of the ET-FES study received the final approval from Liguria Region allowing the start of the approval procedures, which was 4 months after the official start of the project. The first scientific report was due in December 2013 and required a summary of the activities performed on the project on the 1st year, with economic justification. The Slovak Academy of Sciences (SAS) as the TRANSCAN partner responsible for the monitoring of JTC-1 received the report in time.

Clinical Trial Submission and Activation

The study was configured as an academic, interventional clinical trial; the radiopharmaceutical ([^{18}F]- FES) used for PET/CT must comply with the legislation on drugs; current legislation on Clinical Trials must be observed (European directive 2001/20/EC declined in the various Member States, Decree n° 211 for Italy). [^{18}F]-FES is a radiopharmaceutical that is not easily produced and it has no Marketing Authorization yet. On 29th September 2013, clinical ET-FES study protocol was finalized and approved by all the involved partners.

None of the countries could begin the study until approval by the reference Ethics Committee (EC)/Institutional Review

TABLE 1 | Timelines.

Country	Time to EC approval (months)	Time to CA approval (months)	Time to signed contract (months)	Time to 1st patient in (months)	Time from funding to 1st patient (months)
Italy	1.5	8.0	13.0	14.0	20.0
France	2.5	5.0	9.5	10.0	30.0
Spain	2.5	8.5	18.0	28.0	59.0
Germany	13.0	26.0	27.0	31.0	60.0

Board (IRB) had been obtained and until the local regulatory requirements complied with the national competent authorities. The Sponsor provided each Country with the core documents (final protocol, Investigator's brochure, Investigational Medicinal product dossier, subject information sheets, consent forms) (2) and all other relevant study documentation for local required submissions. Patient Informed Consent was completed and translated into the different languages. A trial insurance policy was stipulated. The principal investigators and the Sponsor ensured that the study was conducted in full conformance with the 1964 Declaration of Helsinki principles and with the laws and regulations of the country in which the research was being conducted, whichever afforded the greater protection to the individual. The study had to fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH-E6 Tripartite Guideline (January 1997) and with national laws. For the Study conducted in the EU/EEA countries, the Principal investigator would ensure compliance with the EU Clinical Trial Directive (2001/20/EC), ICH GCP and EU Data Protection Directive (95/46/EC).

In parallel, the development process of [^{18}F]- FES, according to Good Manufacturing Practice (GMP), started in January 2013 and it was completed in November 2013. All the logistics for tracer shipping and delivery had been set up. A Financial contract was put in place between AAA and the project coordinator in order to define the budget and timing for study drug supply. Study drug would be provided to all the Sites (3) from French laboratories. [^{18}F]-FES was defined as Investigational Medicinal Product (IMP). The current "Clinical Trials Directive" defined the requirements for authorization of manufacturing an IMP, which includes applying Good Manufacturing Practices (GMP). Within this regulatory framework, also Good Clinical Practices (GCP) for conducting clinical trials were mandatory, stating responsibilities, requirements, and structure of clinical trials (ICH GCP). The documentation package for a clinical trial application included both information on the IMP as well as on the conduct of the clinical trial itself. All the information concerning the radiopharmaceutical to be used in the trial was included in the Investigational Medicinal Product Dossier (IMPD) (4, 5). The information in the IMPD has to be given in a standardized way, which is based on the so called Common Technical Dossier (CTD) format, which is also used in applications for marketing authorization. The IMPD addressed chemical and pharmaceutical properties covering the quality of a new release criteria, analytical procedures and their validation; in the second part of the IMPD, information on the safety and efficacy of the IMP should be provided (3). Regarding the quality part of IMPD, the Company sent the quality dossier directly to Competent Authorities (CAs) in order to maintain the confidentiality of [^{18}F]- FES production data; therefore the objections from CA would be communicated to the Company only. This process certainly makes the authorization process more complicated as the Sponsor (different from the Company) is not directly involved in the quality IMPD submission and must wait for approval of this part which is not under his direct control and responsibility. The Investigational Medicinal Product Dossier (IMPD) and the Investigator's Brochure (IB) have to be finalized and provided for submission to the CAs by the Clinical Trial Sponsor. Under the Directive, Clinical trial application has to be approved on a national level both by EC/IRB and national CA within defined timelines according to Directive. National radioprotection competent authorities were also involved and there was a very time- consuming procedure related to the high heterogeneity between Countries.

Each National Principal Investigator submitted the study to its own EC/IRB and CA. The ET-FES study was submitted in Italy to the Coordinating EC and CA in December 2013 and it was approved by Coordinating EC in January 2014 while final AIFA approval came on 13th August 2014 and Ministry of Health (radioprotection Office) approval in October 2014. In February 2015 the submission package was sent to France EC/IRB and CA and the final approval came on 01st Jul 2015. On 24th November 2014 the submission package was sent to Spanish EC/IRB and CA and the final approval was released on 08 August 2015 (conditioned approval) by AEMPS. On January 8th 2015 submission package was sent to Germany EC/IRB and CA but the final approval came only in March 2017 (re-submission was required to avoid a refusal due to quality IMPD concerns).

The time to EC approval was 1.5 months for Italy, 2.5 months for France, 2.5 months for Spain, and 13 months for Germany (due to amendment submission). The time to CA approval was: Italy 8 months, Spain 8.5 months, France 5 months, and in Germany 26 months (due to re-submission) (see **Table 1** and **Figure 1**). Overall, no ethical objection was raised by any of the ECs; some minor clinical and methodological issues were raised from the EC/IRB in Germany and Spain. Issues from the CAs were raised in all countries, except France (12 queries in Italy, 21 in Spain, and 34 in Germany), mainly regarding quality aspects of [^{18}F]-FES IMPD (see **Table 2**). At Sponsor level, the time to the final agreement signature with the [^{18}F]-FES manufacturing

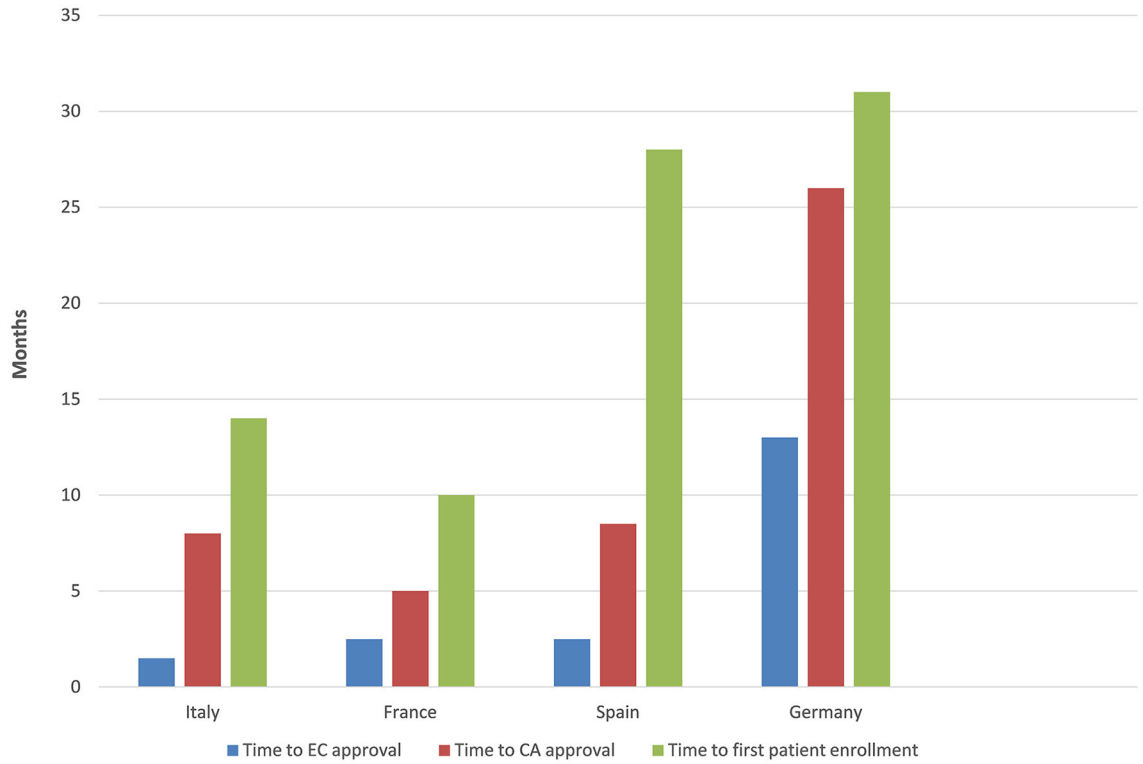


FIGURE 1 | Timelines.

TABLE 2 | Objections by EC and CA.

Country	Objections	
	Ethics committee	**Competent authority**
Italy	-	12 (AIFA)
France	-	0 (ANSM)
Spain	Minor	21 (AEMPS)
Germany	Minor	34 (BFARM)

company required 13 months. After finalization of all contracts and approval by EC and AC, the first patient was enrolled on 6th February 2015 in Italy: this was 14 months after EC submission and 20 months after the official start of the ET-FES project, as set up by the Italian Ministry of Health and communicated to the Joint Call Secretariat (JCS). The time to first patient in was 10, 28 and 31 months from the date of submission in France, Spain, and Germany, respectively (see **Figure 2**).

In particular, in Germany, the main reason for the delay was a difficult and time-consuming approach to get approval by CA for the study (6), which was already enrolling patients in Italy and France; Germany's CA raised several questions concerning the quality aspects (quality IMPD) of the tracer which had been approved to be used in the study in Italy, France and Spain. German CA concerns mainly addressed cold chemical precursor: according to CA request, it should be described and characterized to an extent which was usual for active substances in clinical trials. These changes had to be submitted as Substantial Amendment to the current IMPD and they took time to align the Country specific documentation also for Italy, France, and Spain.

The different timescales for submitting study documents in each Country and the misalignment of objections by each CA, have generated several requests for changes to the study documents with the consequent need to make Amendments; as requested by the 2001/20/EC Directive, the alignment of Core documents is mandatory. This procedure was time consuming and impacted significantly on study activation timelines. In addition, during the entire period of study activation, there was a change in the therapeutic landscape and management of patients with endocrine sensitive MBC. Introduction and approval of CDK 4/6 inhibitors and PI3K-inhibitors in combination with endocrine treatment was recommended by ESMO and national guidelines as the first choice of treatment for first line therapy for HR-positive MBC. This new information was approached with a further Amendment to the clinical protocol. Spain left the project in June 2018 due to funding shortage after enrollment of three out of 10 preplanned patients; France and Italy completed accrual as planned; Germany enrolled eight patients but stopped accrual in 2019. The total number of enrolled patients was 147 out of 310 planned patients (47.4%) of which 88 in Italy, 48 in France, eight in Germany, and three in Spain. Overall accrual was stopped on 22nd January 2021 due to [^{18}F]- FES shortage as the primary

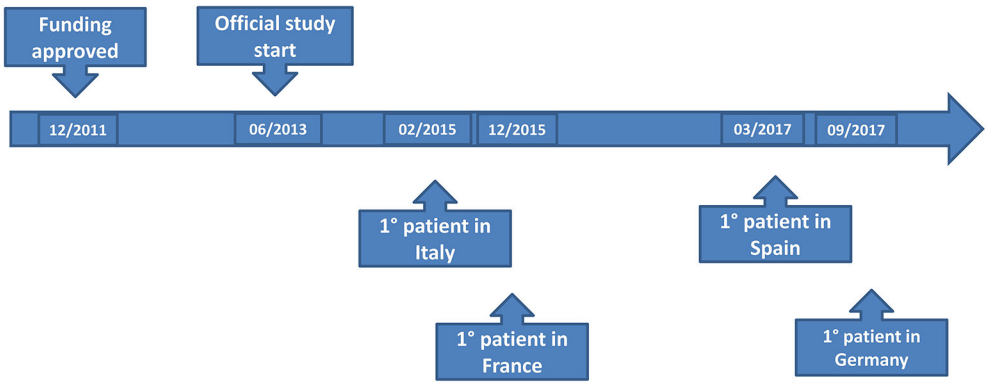


FIGURE 2 | Sites activation.

reason but also for substantially exceeding the project deadlines with consequent exhaustion of the funds allocated for the project.

DISCUSSION

There has been an increasing interest in molecular imaging by experimental radiotracers in oncology. Especially with the approval and introduction into clinical practice of effective but extremely expensive new targeted agents, the sustainability of the cost of these medications is rapidly becoming an emergency in health policies in the EU. For this reason, personalized medicine is quickly becoming an unmet need also in health economics. The possibility of treatment individualization, based on the detection by molecular imaging of the *in vivo* activity of drug targets and pathways, in addition to molecular assessment on tissue biopsies, may represent the missing step in delivering the right (expensive) drug to the patient with the highest benefit. This will also optimize treatment in those patients who are not likely to respond, thus sparing ineffective therapies. However, this process requires the formal validation of these new molecular tracers in well-designed translational trials. These types of trials are particularly difficult in terms of "sustainability" as well. Additionally, the costs of new radiotracers and of high-quality research are high, so dedicated funding is needed and can only be achieved through academic grants. Pharmaceutical companies are of course reluctant in principle to fund research project aimed at treatment individualization if the approval for a wider indication has already been achieved. Academic trials therefore become fundamental for promoting trials which are not attractive to big pharma. To this context, our project could provide additional evidence on the performance of these innovative techniques in treatment individualization based on the results of a randomized clinical trial. Directive 2001/20/EC intended to harmonize clinical trial application but in practice, the regulatory requirements are not really harmonized due to specific regulatory requirements and variability across EU Members States (MS) in particular for innovative drugs including Radiopharmaceuticals. This problem will be overcome by European Regulation 536/2014 that will come into force on 31/01/2022 as the new submission procedure will be centralized. An existing pathway that could has been used to facilitate the process is the Voluntary Harmonization Procedure (VHP), an Initiative of the Clinical Trials Facilitation Group to gain experience in the practical work within the ideas of a "CT- regulation" and to offer an option for sponsors and Member States to achieve harmonized multi-national clinical trials and share workload. From a regulatory perspective, taking into account that the ET-FES trial involves an experimental drug ([^{18}F]-FES), without Market authorization in the EU, the approval process was timely completed at EC level in all the participating institutions but time to CA approval was unexpectedly different in the various countries; this was probably due to a different interpretation of the rules, guidelines and requirements from each local CA, indicating the absence of really harmonized procedures as requested by the 2001/20/EC Directive. Furthermore, additional causes of delay were encountered: in Italy, the critical issue concerned the administrative procedures to activate this type of international EU projects, requiring a suboptimal time span, in order to satisfy all the legal aspects on contracts by public bodies, in Germany some radioprotection concerns further delayed authorization. These issues and timelines need to be considered and solved, when applying for EU calls where the allowed project duration is 3 years. Performing a clinical trial requires a dedicated infrastructure to deal with the administrative and regulatory requirements; for this reason, it may not be accessible for Academia or Collaborative Groups, to deal with national and even more with an international clinical trial. Administrative aspects at local institutions, ECs, ministry of health and other involved agencies were very difficult to approach. This was also due to the fact that in addition to the ERANET programme rules, each center has to obey national laws and regulations concerning Clinical Research. Indeed, in our experience, each regulatory competent authority asked for different modifications of the study protocol, mainly IMPD and Investigator Brochure of [^{18}F]-FES, which we had to solve before starting of the project. It was very difficult and time consuming to align all the changes requested by the national competent authorities; for this reason time elapsed and the study became "old" as new drugs came on the market. Nevertheless, with a strong commitment from all partners we finally overcame almost all

TABLE 3 | Main barrier details and possible solutions.

Issue	Proposed solution	Comments
Documents preparation on a national level cause misalignment	The implementation of a national network for co-operation will facilitate multidisciplinary clinical research, as well as provide guidelines and models of good practices for national support infrastructures.	Even if the scope of Directive 2001/20/CE is to align all study documents, in practical there is eterogeneity
Lack of experienced personnel	Develop training, education and knowledge on clinical research to all the multidisciplinary team will develop a "culture" of clinical research and a professional network of experienced people	All these expertise are involved from clinical protocol writing to final data analysis.
Each National Principal Investigator submitted the study to its own EC/IRB and CA.	Scientific advice and support for non-commercial sponsors should be provided with practical support for trial submissions; all the informations should be available with a forum for academic investigators to share their issues.	New Regulation 536/2014 will hopefully overcome this issue by centralizing trial submission
Approval timelines for EC and AC approvals are legally defined according to European Directive; the different submission timing caused different approval timing.	Same timing of submission to EC and CA	Directive foresees a national approval that will be superseded by Regulation 536/2014
Different CA objections on quality IMPD; CA approval was unexpectedly different in the various countries. Need for Substantial Amendments to align country specific documentation	CA opinions should be the same; regulatory competencies should be shared and implemented in collaboration with the relevant international agencies and ethics committees.	This is caused by different quality guidelines interpretations
Confidential quality data not shared by Company with the Sponsor; this process is not under Sponsor control and responsibility.	Clearly define confidential data policy in terms of ownership and responsibilities between Sponsor and the Company.	The incoming Regulation 536/2014 may probably overcome this issue with co-sponsorship.
Contracts and local administrative item is very time consuming. Every Country was funded by the responsible national funding organization according to their specific regulations	Single contract, centralized economic management	
Time consuming procedures related to the high heterogeneity between National radioprotection competent authorities	Competent Authorities on radioprotection should be aligned at an European level	

the bureaucratic, administrative and regulatory problems and the study was finally activated. Unfortunately the project had only a 3 year duration and the costs could no longer be allocated to the European project. The implementation of a national network for co-operation in clinical science would facilitate multidisciplinary clinical research, as well as provide guidelines and models of good practices for national support infrastructures. Hub and spoke networks of oncological centers, along with a multidisciplinary approach, is the winning strategy to offer additional skills and expertise through the involvement of different specialists not always heavily involved in clinical research. In this project, in particular, nuclear medicine is a crucial aspect and the standardization of image acquisition protocols is one of the most important requirements among network participating centers. It's important that the hub of the network provides a dedicated infrastructure to harmonize the roles and responsibilities, facilitate the communication between the trial promoter and each center/ethical committee/national and local competent authority, supervise the timing of each step and provide help in those centers requiring expertise and support for specific duties related to the trial. Furthermore, it should produce and diffuse specific guidelines to enhance the comparability of data acquired by molecular imaging and to boost molecular imaging so that it becomes a standard diagnostic modality in future clinical medicine and research (7, 8).

Main barriers to speeding up the process and the possible solutions can be categorized in three main areas:

1) **Administrative complexity**:
   a. **Approval at European level**—an experienced grant office is needed to speed up the submission in particular for the national funding aspects.
   b. **EC and CA approval**—even if the scope of European Directive was to align all study documents, in practical there is eterogeneity; documents should be centralized and made available for all researchers with a forum for academic investigators to share their issues. The regulatory competencies should be shared and implemented in collaboration with the relevant international agencies and ethics committees. Scientific advice and support for non-commercial sponsors should be provided with practical support for clinical trial submissions through an easy to-follow flow chart and guidelines.
   c. **Local feasibility approval**—for administrative and economic items there is an urgent need for a centralized management; for radioprotection, the new Directive 2013/59/Euratom should facilitate but an alignment by all Competent Authorities on this topic is needed.
2) **Heterogeneous staff training**: Developing training, education and knowledge in clinical research for whole

the multidisciplinary team will further a "culture" of clinical research and create a professional network of experienced people.

3) **Infrastructure support**: The presence of adequate personnel within regulatory and legal office, grant office, radio pharmacy, clinical trial office (study coordinator and biostatisticians) is the winning strategy to reach the goal. All these expertise are involved from clinical protocol writing to final data analysis. National institutions should promote the development of clinical research infrastructures with the above competences and support functions organized in networks of research units and investigators.

A summary of main barriers details and possible solutions are reported in **Table 3**. All these barriers and realistic timelines must be taken into account when evaluating project feasibility, before applying for an European grant.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRST and Romagna Ethics Committee (CEIIAV). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM and TD contributed for regulatory aspects, acquisition of data, and drafting the manuscript. NH, EB, RW, JC, AP-G, and CS contributed to the study design and conception of the study. JA, AP, FM, HI, LB, and ON contributed to study design. AG contributed to the study design, conception of the study, and project coordination. VD contributed to IMPD data. MP, AA, MI, DC, and GR contributed to project starting procedures. All authors provided substantial input in the study design, critical revision of the manuscript, and read and approved the final manuscript.

FUNDING

This research received grants from ERANET JTC 2011.

ACKNOWLEDGMENTS

The authors specifically acknowledge the continued support and flexibility of the respective national grant giving agencies which was essential for conducting of this trial.

REFERENCES

1. Parrish MC, Tan YJ, Grimes KV, Mochly-Rosen D. Surviving in the valley of death: opportunities and challenges in translating academic drug discoveries. *Annu Rev Pharmacol Toxicol.* (2019) 59:405–21. doi: 10.1146/annurev-pharmtox-010818-021625
2. Schwarz SW, Decristoforo C, Goodbody AE, Singhal N, Saliba S, Ruddock P, et al. Harmonization of United States, European Union and Canadian first-in-human regulatory requirements for radiopharmaceuticals - is this possible? *J Nucl Med.* (2018) 2018:jnumed.118.209460. doi: 10.2967/jnumed.118.209460
3. Kolenc Peitl P, Rangger C, Garnuszek P, Mikolajczak R, Hubalewska-Dydejczyk A, Maina T, et al. Clinical translation of theranostic radiopharmaceuticals: Current regulatory status and recent examples. *J Labelled Comp Radiopharm.* (2019) 62:673–83. doi: 10.1002/jlcr.3712
4. Verbruggen A, Coenen HH, Deverre JH, Guilloteau D, Langstrom B, Salvadori PA, et al. Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU. *Eur J Nucl Med Mol Imaging.* (2008) 35:2144–51. doi: 10.1007/s00259-008-0853-7
5. Decristoforo C, Schwarz SW. Radiopharmacy: regulations and legislations in relation to human applications. *Drug Discov Today Technol.* (2011) 8:e71–7. doi: 10.1016/j.ddtec.2011.11.012
6. Monti M, Corradengo D, Nanni O, Piccardo A, Matteucci F, Brain E, et al. ERA-Net TRANSCAN JTC 2011: critical aspects of the startup procedures of an International Academic Clinical trial (ET-FES), funded by the European Community (EC) and coordinated by an Italian Institution. *Ann Oncol.* 27(Suppl.4):iv107–25. doi: 10.1093/annonc/mdw345.22
7. Ussi A, Migliaccio G. The EMA framework of collaboration with academic stakeholders. *Mol Ther.* (2016) 24:1883–4. doi: 10.1038/mt.2016.187
8. Starokozhko V, Kallio M, Howell AK, Salmi AM, Andrew-Nielsen G, Goldammer M, et al. Strengthening regulatory science in academia: STARS, an EU initiative to bridge the translational gap. *Drug Discov Today.* (2021) 26:283–8. doi: 10.1016/j.drudis.2020.10.017

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Medicine

ORIGINAL RESEARCH
published: 20 January 2022
doi: 10.3389/fmed.2021.811855

The Added Value of Patient Engagement in Early Dialogue at EMA: Scientific Advice as a Case Study

Aisling Murphy[1,2†], *Nathalie Bere*[1†], *Spiros Vamvakas*[1] *and Maria Mavris*[1*]

[1] *European Medicines Agency, Amsterdam, Netherlands,* [2] *GlaxoSmithKline, London, United Kingdom*

The European Medicines Agency provides Scientific Advice to medicines developers and patient input has been an integral part of this process for many years. As end users of medicines, patients bring their perspectives to many different processes along EMA's regulatory pathway, complementing the scientific expertise. While the value of including patients has been well-demonstrated over the years, requests for evidence of their impact continue. Using Scientific Advice as a case study, data was collected over a four-year period to assess the number of patients involved, where they contributed, as well as the impact and added value of their input. In this paper, we show that patients' contributions have a tangible impact on the recommendations provided to developers and in over half of the cases, this led to further discussion on relevant patient perspectives. These data provide quantitative evidence of the value of patient input in medicines development and supports EMA's continued inclusion of their voice throughout the medicine's lifecycle.

Keywords: scientific advice (SA), regulation, medicines, patient engagement (PE), added value

OPEN ACCESS

Edited by:
Hubert G. Leufkens, Utrecht University, Netherlands

Reviewed by:
Kerstin Margareta Westermark, Uppsala University, Sweden
Carla Matos Torre, University of Lisbon, Portugal
Christine Gispen-de Wied, Gispen4RegulatoryScience, Netherlands

***Correspondence:**
Maria Mavris
maria.mavris@ema.europa.eu

[†] *These authors share first authorship*

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *09 November 2021*
Accepted: *30 December 2021*
Published: *20 January 2022*

Citation:
Murphy A, Bere N, Vamvakas S and Mavris M (2022) The Added Value of Patient Engagement in Early Dialogue at EMA: Scientific Advice as a Case Study. Front. Med. 8:811855. doi: 10.3389/fmed.2021.811855

INTRODUCTION

Scientific advice is an important tool in the medicine regulatory lifecycle (1, 2). The European Medicines Agency (EMA) began offering scientific advice in 1996 to provide guidance to medicine developers on all aspects of the development programme from quality of the manufacturing process, to non-clinical and clinical aspects including methodological issues. The Scientific Advice Working Party (SAWP) makes recommendations in response to questions posed by medicines developers. Scientific advice aims to support developers to provide robust evidence for benefit–risk assessment at the time of marketing authorisation application (MAA), thereby facilitating the introduction of new, safe and effective medicines (3). While scientific advice is voluntary and non-binding, compliance with the recommendations has been shown to correlate with successful MAAs (4). Scientific advice is one of the earliest activities where EMA began engagement with patients.

Patients, as end users of medicines are key stakeholders of the Agency and are invited to contribute to EMA's work based on their experience of living with a particular condition and its treatment. The importance of involving patients in all aspects of medicines development is no longer disputed, yet questions concerning how best to capture and use their input and how to measure their impact are still being raised.

EMA has been actively engaging with patients since its creation in 1995, beginning with informal discussions with patient groups that have now evolved to more formalised interactions as set out in the Framework for interaction with patients and their organisations (5, 6).

Patient engagement has evolved and diversified over the years in parallel with the expansion of EMA's remit. There are several categories of patient representation at EMA; those who represent all patients in the European community as members of the EMA Management Board and scientific committees; those who represent their organisation via membership of EMA's Patients' and Consumers' Working Party (PCWP) or participation in workshops and responding to EMA public consultations. Finally, patients represent themselves as individual experts for medicine-related activities such as scientific advice, scientific advisory groups (SAGs) and the review of documents destined for the public such as medicines overviews, safety communications and package leaflets (7). Various engagement methodologies have been tested and implemented over the years, resulting in established procedures to include the patient voice all along the medicines regulatory lifecycle at EMA (8).

Patient involvement in scientific advice began in 2005 when rare disease patients requested to be involved in protocol assistance procedures for medicines with an orphan designation. Success of this activity led to the inclusion of patients in scientific advice for medicines without an orphan designation from 2013 as well as parallel procedures of scientific advice and health technology assessment (HTA) bodies (**Figure 1**). The term "scientific advice procedures" will be used to encompass scientific advice, protocol assistance (applicable to orphan medicines only) and parallel EMA/HTA bodies consultations (9).

Scientific advice was selected as EMA has many years of experience engaging with patients in this area, there is a good data set covering several years that represents a collaborative activity within EMA as well as with patient groups. A steady increase of patient involvement in scientific advice procedures has been observed over the years correlating with the increase in requests for scientific advice to EMA (8) and the increased efforts made by EMA for patient involvement. In this study we show the added value of patients' contributions to medicines development as well as to a broader understanding of living with the condition.

METHODOLOGY

Identification of Scientific Advice Procedures for Patient Input

Scientific advice requests that would benefit from patient involvement were identified during monthly meetings with EMA scientific advice office. Not all procedures required patient participation if, for example, advice is only sought on non-clinical, regulatory or statistical issues. Individual patients were invited primarily to comment on clinical aspects, such as comparator treatments, endpoints and patient populations in prospective clinical studies as these relate to the objectives and feasibility of the clinical studies.

Identification of Patients

EMA works with a diverse group of EU patient organisations that meet strict eligibility criteria with respect to representation, funding and transparency (10). The term patient is used to encompass patients, consumers or carers. Patients may be identified and contacted through an EMA eligible patient organisation or via an EMA database of individuals, established in 2016, who wish to participate in EMA's activities. Patients who have registered their interest in participating may be contacted directly when a procedure in their disease area of interest arises. Currently more than 180 organisations and 500 individuals are registered in EMA's stakeholder database.

Criteria for Patient Involvement

There are several criteria that were used to select patients; usually one and sometimes two patients are invited to participate in a scientific advice procedure. English is the working language at EMA, and all patients must have a level of understanding that would enable them to read the relevant documents and comment in writing or in person. Depending on the questions raised, the level of experience can vary from a newly diagnosed individual, a carer or a long-term patient advocate representing the condition. Having followed a training course on medicines' development is beneficial but not a pre-requisite for involvement. As with all other experts participating in EMA activities, patients were required to complete a confidentiality agreement and declare any competing interests, which were assessed prior to formal invitation. EMA experts were generally residents of an EU Member State.

Collection of Feedback and Analysis of Patient Input

The EUSurvey tool (European Commission's official survey management) was used to create a survey and collect data related to patient involvement. The survey was created with colleagues in the EMA scientific advice team and contained 11 questions (**Annex I**).

The first part of the survey asks about the coordinators' perspective, whether they had any interactions, in writing or by telephone, with the patient prior to their participation in the procedure. This also included whether the patient was adequately prepared (with respect to their role and understanding of the procedure) as well as the areas where patient input was sought. Terminology used in the survey was consistent with terms used and understood by all coordinators. EMA colleagues responsible for specific scientific advice requests, referred to as procedure coordinators, were sent a survey at completion of each procedure (Day 40 for written procedures or Day 70 for procedures where a meeting was held).

Patients were also sent a survey (created in EUSurvey) at completion of each procedure to gather their perspectives on their involvement in the scientific advice procedure (**Annex II**). The survey was sent to patients at completion of each procedure along with a letter of thanks for their participation, meeting minutes (in the case a meeting was held) and the final letter of advice sent to the medicine developer. No personal data was collected via the surveys. Questions to the patients included whether what was expected of them was clear, if they had enough opportunity to contribute to the procedure and if they felt their comments were considered during the activity. As responding to the survey is voluntary, EMA did not follow up to obtain feedback unlike with the surveys completed by coordinators.

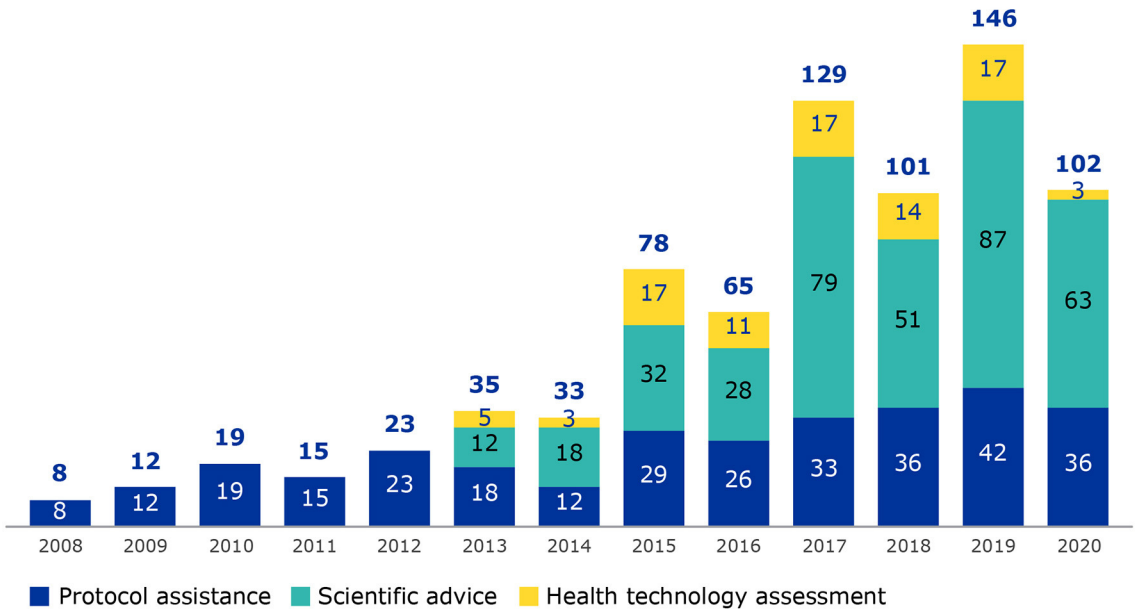


FIGURE 1 | Number of patients involved from 2008 to 2020, by procedure type (protocol assistance, scientific advice and parallel procedures with HTA bodies). Data collection on patient involvement in scientific advice procedures began in 2008.

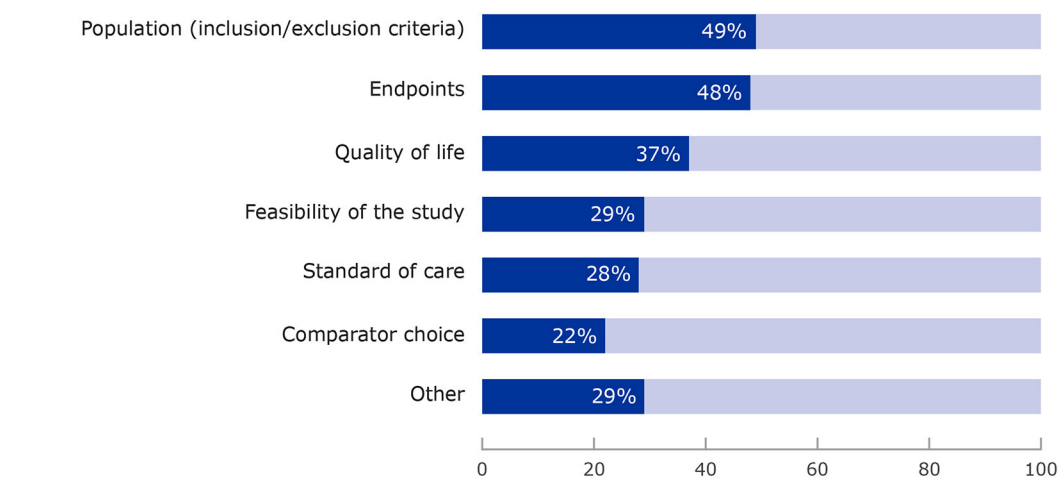


FIGURE 2 | Areas of development plan where patients provided input. More than one category could be selected for each survey question.

Data Analysis

A total of 371 survey responses were received from the procedure coordinators for the four-year study period. Analyses were performed using aggregated data for each survey question. To determine the percentages shown in **Figures 2**, **3**, the total number of responses received for each question was divided by the total number of survey responses received ($n = 371$) to ensure a consistent denominator. Several survey questions allowed more than one response.

RESULTS

Responses to Surveys by EMA Procedure Coordinators

For the study period of 2017–2020, a total of 371 survey responses were received for the 478 patients (78%) who were involved in scientific advice procedures related to clinical development (11). The results for each year, 2017 (90/129; 70%), 2018 (75/101; 74%), 2019 (110/139; 79%) and 2020 (96/102; 94%), show high response rates. On average patients are involved in one

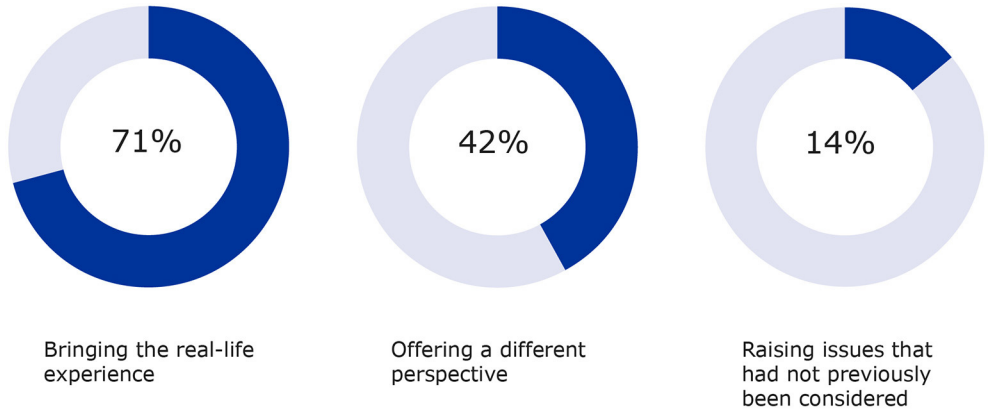


FIGURE 3 | Additional input by patients on aspects such as real-life experience, different perspectives and other considerations were also measured (2017–2020).

in five (20%) scientific advice procedures that include clinical questions (8).

Contact With the Patients

The majority of coordinators (91%) contacted the patients prior to their involvement to explain the process of scientific advice and where their input would be helpful.

Areas for Patient Input

Requests by coordinators focused primarily on aspects such as study population (77%), endpoints (74%), study feasibility (52%), quality of life (48%) and other aspects such as patient-reported outcomes, biomarkers and safety issues.

Where Patients Made Contributions

Figure 2 shows that patients most often commented on the selection of the clinical trial population (49%), the choice of endpoints (48%), study feasibility (52%), quality of life studies (48%), and also bringing in a real-life perspective of living with a condition (as patient or carer), offering a perspective different to the medical and scientific experts and raising issues that had not previously been considered by the Scientific Advice Working Party. "Other" areas included general insights into the condition, its daily impact and treatment options. Overall, input resulted in further reflection by the working party in more than half of the cases (52%).

The survey also measured whether the recommendations provided to the developer were modified as a result of patient input. The results showed that the final advice letter was modified in 20% of cases based on patient contributions. Importantly, the vast majority of cases where patient input did not change the final advice, is correlated to the fact that patients agreed with the proposed development plan.

The added value of patient input was measured for the areas listed in **Figure 3** with "bringing the real-life experience of living with a condition and its treatment" ranking highest (71%), followed by "offering a different perspective" being outlined (42%) as well as "raising issues that had not previously been considered" (15%). These aspects complement the contributions to the specific questions raised by the developers on the clinical trial aspects and contribute to future recommendations in the same therapeutic area.

Responses to Surveys From Patients

EMA also received 125 survey responses from participating patients for the same reporting period. Participants could contribute to a scientific advice procedure in writing or in person when a meeting with the medicine's developer was organised.

Participation in scientific advice: almost equally split between contributing in writing (49%) or attending a meeting (51%). There was some overlap as some patients who attended meetings also provided comments in writing.

In most cases (86%), patients responded that they understood what was expected of them in terms of their written contribution and 83% felt that they were able to provide input to the issues raised in the scientific advice request.

Patients who attended meetings (in person or virtually) reported in 90% of cases that they understood what was expected of them in the meeting and felt in 92% of the cases that they had an opportunity to provide input to the discussion.

Overall 75% of patients felt their comments were taken into account, both in writing and while attending meetings but when looking at the breakdown, there is a higher response rate (86%) when patients attended meetings compared with 76% when contribution was only sought in writing.

The majority of patients (80%) felt positive about their overall experience of participation. The main barriers identified by patients were the complexity of the information to review and the short deadlines for contributing particularly during written procedures.

DISCUSSION

In this paper we describe the contributions and added value of patient participation in scientific advice procedures at EMA, which has not previously been assessed in a quantifiable manner. We describe the methodology used to involve patients in

scientific advice and present an analysis of feedback received from the EMA procedure coordinators as well as the patients who have participated.

While regulators and other experts can provide guidance on many aspects of the complexities of medicine development, the day to day experience of living with a condition and its treatment can only be addressed by someone with first-hand experience. The data presented here offers unique insights as it is the first time that such impact data is being presented by a regulatory body. We have highlighted how patients fill an important gap by providing real-life experience of the conditions and their treatments, in addition to providing input into the clinical aspects of the development plans.

As a result of patient input, one in five scientific advice responses provided to the medicines' developers were modified and in 90% of the cases where no modification was made, patients agreed with the proposed development plan. Overall, their contributions led to additional reflection by the EMA procedure coordinators in more than half of the cases. This demonstrates that there are two levels of impact which can be considered; first where patients input results in a change to the recommendations provided by a medicines' regulator to a developer, second where patients agree with a proposed development plan, therefore not necessitating additional changes to the advice given. In addition, patients who were contacted prior to the procedure starting appeared to be better prepared than those who were not.

Our analysis supports the continued involvement of patients in scientific advice and illustrates the importance of including this stakeholder group in early dialogue between regulators and medicines' developers. There is clear alignment of both EMA procedure coordinators and patient participants that patient involvement in this activity is beneficial. In nearly all cases, EMA procedure coordinators indicated that patient participation was of added value and the majority of patients felt that their comments were impactful.

The authors acknowledge that further analysis could be performed on survey responses per therapeutic area of conditions for which scientific advice was sought. Another limitation to acknowledge is that the patients involved in the procedures across the years were not always the same and a diversity of experience and input would be observed due to the mix of those who were new to EMA activities and those more experienced patient experts. While the questions related to the different aspects of the development plan are clear well-defined for the scientific coordinators, questions related to the additional value brought by patients such as "bringing the real-life experience", "offering a different perspective" and "raising issues not previously considered" could be considered subjective and thus open to interpretation by individual coordinators.

The feedback from patients is also encouraging. One respondent described their involvement as "a highlight in 17 years of patient advocacy work" and another commented "I really appreciate the relevance EMA gives to patients" voice in the procedures. Taking into consideration our opinion from the beginning, it is beneficial for all stakeholders'.

The complexity of the information on which patient input is sought and the regulatory timelines of scientific advice were difficulties raised by some respondents. EMA aims to lessen this as much as possible by asking patients to focus on the sponsor's clinical questions and by providing one-to-one individual support throughout the procedure. Importantly, our analysis shows that patients were more likely to be more prepared to participate when they had been contacted by the EMA procedure coordinator prior to their involvement. The importance of prior contact is crucial as it allows for better preparation and thus more meaningful contributions by patients. In addition to one-to-one support provided by EMA staff, patients participating in EMA activities can benefit from various multimedia training resources online (12). EMA also holds stakeholder training days where attendees participate in interactive small group sessions on various regulatory activities including scientific advice.

We acknowledge that the involvement of only one or in some cases two patients per procedure can mean that the views expressed are not necessarily representative of the entire patient community in a given disease area. EMA is exploring additional methods to gather input from the wider patient community. Following the publication of a patient preference study involving multiple myeloma patients in 2016 (13), EMA is exploring the feasibility of conducting similar studies in other disease areas. EMA also collaborates with the IMI-PREFER project, a consortium of stakeholders who have explored the use of patient preference studies in regulatory, academic and industry settings (14). In addition, the Agency is examining the possibility of facilitating focus groups to gather the opinions of several patients on a given topic. The use of focus groups and patient preference elicitation will complement rather than replace one-to-one discussions involving individual patients. Each methodology has value and addresses different needs. Together these activities will help to further develop and strengthen the patient voice in regulatory procedures, which is further reinforced by the recommendations in the EMA Regulatory Science to 2025 (15) and comments received during the public consultation (16).

It is important to bear in mind that patients contributing at European level can also provide their expertise at national level. We hope our findings encourage national competent authorities who have not yet involved the patient voice in their procedures to explore this possibility.

CONCLUSIONS

Our analysis illustrates how patient input enriches and complements the medical and scientific discussions in EMA scientific advice procedures. Patients provide their perspectives on a wide spectrum of clinical questions posed by medicines' developers. Patient input adds value in many ways as they offer a different perspective to other experts; they bring experience of living with the condition and its treatment into the discussion. They raised issues that had not been previously considered and, in some cases, they agreed that regulators and developers are taking the right steps. Impact is not only measured by making changes or disagreeing with the recommendations. Importantly we have demonstrated that patients' contributions to these

procedures make a difference and that their suggestions lead to concrete additions to the final scientific advice issued.

The added value of patient input is not exclusive to scientific advice procedures and they are involved in other regulatory procedures such as scientific advisory groups and in consultations by EMA committees, which are both systematic and evolving at EMA. Thus, the demonstrated value of patient inclusion in scientific advice not only supports EMA's continued inclusion of the patient voice throughout the medicine's lifecycle and the diversification of activities where patients participate, but also provides tangible evidence of impactful importance of engaging with patients. There is a need to further expand patient input to real-world evidence, patient reported outcomes, patient preferences and patient experience data, which can only be to the benefit of public health in the EU.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data contain commercial confidential information as well as identifiable patient data. Analysed data can be shared but not raw data. This research did not require ethics approval or informed consent. Requests to access the datasets should be directed to maria.mavris@ema.europa.eu.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants was not required to participate in this study in accordance with the European Legislation and the Institutional Requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

ACKNOWLEDGMENTS

We would like to acknowledge all the patients that participated in this study and for all their contributions to the work of the European Medicines Agency. We thank the coordinators for completing the surveys and for considering patient input in their procedures. We would also like to acknowledge the work of Marcia Martins on the graphics for the figures used in the article as well as Iordanis Gravanis and Jane Moseley for their review.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.811855/full#supplementary-material

REFERENCES

1. Scientific Advice and Protocol Assistance. Available online at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance.
2. From laboratory to patient: the journey of a medicine assessed by EMA. Available online at: https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf.
3. Hofer MPJC, Zafiropoulos N, Vamvakas S, Vetter T, Regnstrom J, Hemmings RJ. Regulatory watch: impact of scientific advice from the European Medicines Agency. *Nat Rev Drug Discov.* (2015) 14:302–03. doi: 10.1038/nrd4621
4. Regnstrom J, Koenig F, Aronsson B, Reimer T, Svendsen K, Tsigkos S, et al. Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur J Clin Pharmacol.* (2009) 66:39–48. doi: 10.1007/s00228-009-0756-y
5. Revised framework for interaction between the European Medicines Agency and patients and consumers and their organisations. Available online at: https://www.ema.europa.eu/en/documents/other/revised-framework-interaction-between-european-medicines-agency-patients-consumers-their_en-1.pdf2014.
6. Garcia Burgos J, Moulon, I. Patient contribution to medicines regulation: the EMA approach. *Pharmazeutische Medizin.* (2014) 16:4–8. Available online at: https://media.zwp-online.info/archiv/pub/5332bb88930f2/#6
7. Getting Involved. Available online at: https://www.ema.europa.eu/en/partners-networks/patients-consumers/getting-involved.
8. Stakeholder Engagement Report. Available online at: https://www.ema.europa.eu/en/partners-networks/patients-consumers/key-documents#annual-reports-section.
9. Parallel consultations from regulators and HTA bodies. Available online at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance#parallel-consultations-from-regulators-and-hta-bodies-section.
10. Criteria to be fulfilled by patient, consumer and healthcare professional organisations involved in European Medicines Agency (EMA) activities. Available online at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/criteria-be-fulfilled-patient-consumer-healthcare-professional-organisations-involved-european_en.pdf.
11. Annual Report 2020: The European Medicines Agency's contribution to science, medicines and health in 2020. Available online at: https://www.ema.europa.eu/en/documents/annual-report/2020-annual-report-european-medicines-agency_en.pdf2020.
12. Training and resources for patients and consumers. Available online at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000575.jsp&mid=WC0b01ac058077ce81.
13. Postmus D RS, Bere N, van Valkenhoef G, Galinsky J, Low E, Moulon I, et al. Individual individual trade-offs between possible benefits and risks of cancer treatments: results from a stated preference study with patients with multiple myeloma. *Oncologist.* (2018) 23:44–51. doi: 10.1634/theoncologist.2017-0257
14. Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER). Including the patient perspective. Available online at: http://www.imi-prefer.eu/about/.
15. EMA Regulatory Science to 2025. Available online at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf.
16. Hines PA, Gonzalez-Quevedo R, Lambert AI, Janssens R, Freischem B, Torren Edo J, et al. Regulatory science to 2025: an analysis of stakeholder responses to the European Medicines Agency's Strategy. *Front Med.* (2020) 7:508. doi: 10.3389/fmed.2020.00508

Conflict of Interest: AM conducted the first year of research during her traineeship at EMA and subsequently was employed with GlaxoSmithKline, United Kingdom.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Medicine

ORIGINAL RESEARCH
published: 17 May 2022
doi: 10.3389/fmed.2022.868040

Global Research Trends of Gender-Related Artificial Intelligence in Medicine Between 2001–2020: A Bibliometric Study

Ha Young Yoon[1], *Heisook Lee*[2], *Jeong Yee*[1]* *and Hye Sun Gwak*[1]*

[1] College of Pharmacy and Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul, South Korea,
[2] Korea Center for Gendered Innovations for Science and Technology Research, Seoul, South Korea

This study aimed to assess the research on medical Artificial intelligence (AI) related to sex/gender and explore global research trends over the past 20 years. We searched the Web of Science (WoS) for gender-related medical AI publications from 2001 to 2020. We extracted the bibliometric data and calculated the annual growth of publications, Specialization Index, and Category Normalized Citation Impact. We also analyzed the publication distributions by institution, author, WoS subject category, and journal. A total of 3,110 papers were included in the bibliometric analysis. The number of publications continuously increased over time, with a steep increase between 2016 and 2020. The United States of America and Harvard University were the country and institution that had the largest number of publications. Surgery and urology nephrology were the most common subject categories of WoS. The most occurred keywords were machine learning, classification, risk, outcomes, diagnosis, and surgery. Despite increased interest, gender-related research is still low in medical AI field and further research is needed.

Keywords: artificial intelligence, bibliometric analysis, gender, medicine, medical research

OPEN ACCESS

Edited by:
Mette Due Theilade Thomsen, PIP Adviser, Denmark

Reviewed by:
Elizabeth Pollitzer, Portia, United Kingdom
Mohamed Abouzid, Poznan University of Medical Sciences, Poland

***Correspondence:**
Hye Sun Gwak
hsgwak@ewha.ac.kr
Jeong Yee
jjhello1@naver.com

Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *02 February 2022*
Accepted: *27 April 2022*
Published: *17 May 2022*

Citation:
Yoon HY, Lee H, Yee J and Gwak HS (2022) Global Research Trends of Gender-Related Artificial Intelligence in Medicine Between 2001–2020: A Bibliometric Study. Front. Med. 9:868040. doi: 10.3389/fmed.2022.868040

INTRODUCTION

Gender medicine investigates the influence of sex/gender on the pathophysiology, prevention and treatment of disease, and the social and psychological aspects of illness (1, 2). Although medical research has been performed dominantly on men both in preclinical and clinical studies (3), there have been continuous efforts to overcome this gender bias (4). Since Healy B proposed gender differences in clinical outcomes (5), the subject has been discussed extensively, including in medical fields such as cardiovascular and gastrointestinal disease and oncology (6–9).

Artificial intelligence (AI) is a branch of computer science in which machines are developed to mimic human intelligence, including cognition, perception, and problem-solving (10, 11). This field has developed quickly and been applied to many areas, including medicine (11, 12). With its sophisticated algorithms, AI assists doctors and health professionals with data management, image-based diagnostics, robotic surgery, prediction models, and decision-making support (13, 14).

The widespread application of AI has promoted research in related fields, supporting the implementation of AI technologies in health care (14). Guo et al. found that publications on health

care related to AI increased an average of 17% per year since 1995, with a steep increase of 45% between 2014 and 2019 (15). Along with the increased number of publications in medical AI, gender differences are important in other research areas. As bibliometric analysis quantitatively analyzes scientific publications, it can provide researchers and stakeholders with a macroscopic overview of research trends and help develop further research direction and policy. This study aims to assess the research activity on medical AI related to sex/gender and explore the global research trends over the past 20 years.

METHODS

We extracted bibliographic data on gender-related medical AI articles from Web of Science (WoS) Core Collection. WoS Core Collection, which contains over 20,000 peer-reviewed, high-quality journals published worldwide covering various fields (16), is one of the most well-established and commonly used databases for bibliometric analysis (17, 18). Articles from 2001 to 2020 were collected using the following search terms: {TS=("artificial intelligence" OR "machine intelligence" OR "artificial neural network*" OR "machine learning" OR "deep learn*" OR "natural language process*" OR "robotic*" OR "thinking computer system" OR "fuzzy expert system*" OR "evolutionary computation" OR "hybrid intelligent system*")} AND {TS=(disease* OR illness OR health-related OR medic* OR "medical diagnosis" OR treatment OR health* OR wellness OR well-being OR prescription OR drug)} AND {TS=(gender OR sex OR male OR female)}.

The inclusion criteria were: (i) articles, review articles, and editorial materials; (ii) publications from 2001 to 2020; and (iii) full texts published in English. Articles were excluded if they were a proceeding paper, meeting abstract, book review, book chapter, or correction.

For bibliometric analysis, we extracted the title, abstract, year of publication, journal name with impact factor, authors, institution, country, WoS subject category, keywords, and number of citations. We determined the annual publication growth, the relative research interest (RRI), and percentage of gender-related articles in the medical AI area. Four 5-year periods (2001–2005, 2006–2010, 2011–2015, and 2016–2020) were used to compare the progress of each country. Two bibliometric indicators, Specialization Index (SI) and Category Normalized Citation Impact (CNCI), were computed by InCites with the following equation (19, 20):

$$SI = \frac{Share\ (\%)\ of\ publications\ of\ region\ X}{Share\ (\%)\ of\ world\ publications\ in\ the\ same\ field}$$

$$CNCI = \frac{Observed\ citation\ rate\ of\ region\ X}{Expected\ citation\ rate\ in\ the\ same\ field,\ year,\ and\ documentation\ type}$$

We also analyzed the publication distributions by institution, author, WoS subject category, and journal. We used VOSviewer (Leiden University, Leiden, The Netherlands; version 1.6.11) to draw network visualization maps and performed a citation analysis to identify the most cited articles.

RESULTS

Publication Growth

We identified 3,261 papers during the search (**Figure 1**). After excluding 44 non-English papers and 107 non-articles, 3,110 papers met the inclusion criteria. The graphs of absolute number of publications (**Figure 2A**) and RRI (**Figure 2B**) showed that the overall trend of publication increased from 2001 to 2020. The growth rates from 2001 to 2005, from 2006 to 2010, from 2011 to 2015, and from 2016 to 2020 were 71.4, 115.8, 146.2, and 453.3%, respectively. The number of publications increased steeply between 2016 and 2020, accounting for 77.5% (2,410/3,110) of all included papers. **Figure 2C** shows the percentages of gender-related articles in medical AI researches, which doubled to 6.5% from 2001 to 2020. The linear regression analysis showed that the percentages increased significantly over the last 20 years ($t = 12.978$, $P < 0.001$).

Distribution by Country

Table 1 lists the top 20 countries which published gender-related articles in medical AI between 2001 and 2020. The United States of America (USA) had the most publications on gender-related medical AI ($n = 1{,}377$; 44.3%), followed by People's Republic of China (Peoples R China, $n = 305$; 9.8%), United Kingdom ($n = 241$; 7.7%), Italy ($n = 211$; 6.8%), and the Republic of Korea (South Korea, $n = 201$; 6.5%). Across the four five-year periods from 2001 to 2020, there was a 43.6% increase in the number of publications worldwide from the first to the last period. Canada had the greatest percentage increase in the number of publications (+134.0%), followed by Peoples R China (+127.5%), the South Korea (+77.5%), and United Kingdom (+65.0%). There was no country where the number of publications decreased.

The SIs and CNCIs varied across countries and over time. The global CNCI increased steadily from 1.1 to 1.49 over the last 20 years. Compared to the first period (2001–2005), the USA, United Kingdom, South Korea, and Netherland showed

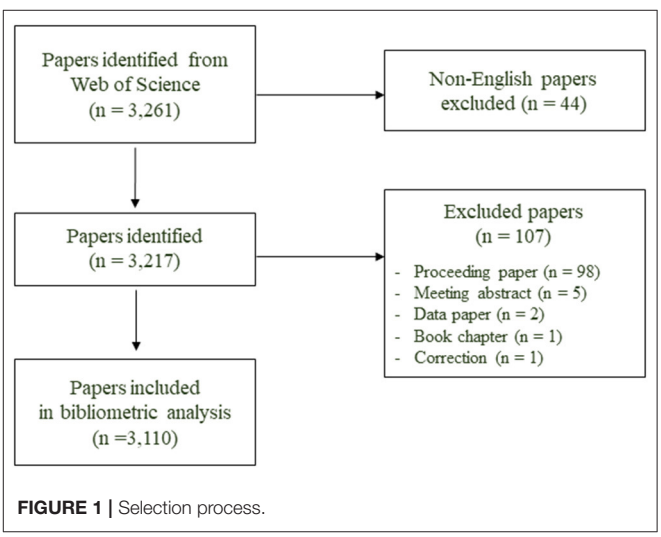


FIGURE 1 | Selection process.

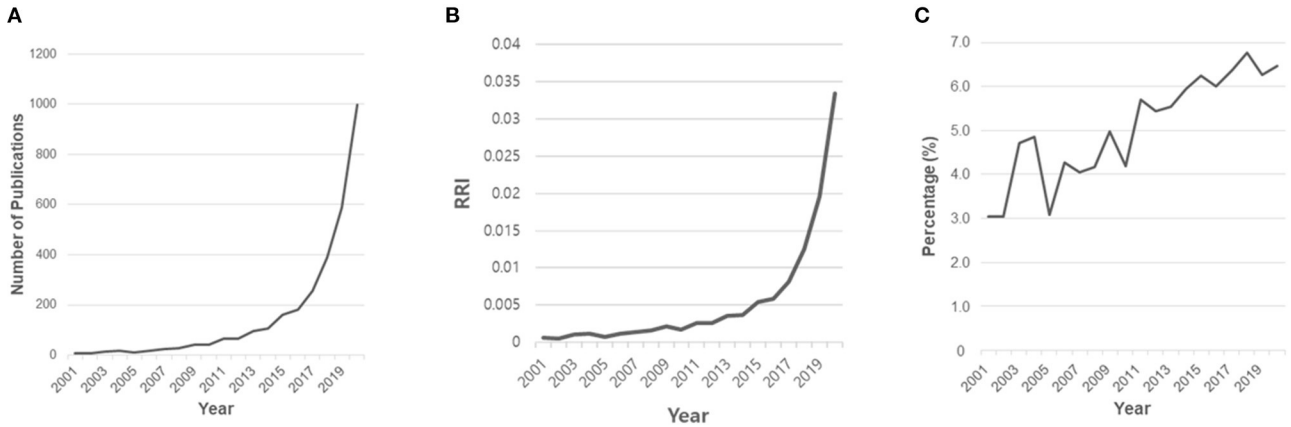


FIGURE 2 | Annual growth of gender-related publications in medical AI. **(A)** The number of publications by year. **(B)** Relative research interest by year. **(C)** The percentage of gender-related publications in medical AI.

an increase in both SI and CNCI in the fourth period (2016–2020), whereas Peoples R China, Turkey, and Japan showed a decrease in their SIs and CNCIs. From 2016 through 2020, South Korea had the highest SI (2.42), whereas Belgium had the highest CNCI (4.11).

Distribution by Institution

Table 2 shows the top 10 institutions for gender-related articles in medical AI fields. The top 10 institutions contributed to 26.5% (824/3,110) of the total number of publications. Harvard University had the largest number of publications (n = 142; 4.6%), followed by the University of California System (n = 136; 4.4%), the University of Texas System (n = 84; 2.7%), Harvard Medical School (n = 84; 2.7%), and University of London (n = 81; 2.6%). Almost 90% of the top 10 institutions were located in the USA.

Figure 3 shows the collaboration network between institutions. The network map of institutions that had at least 20 publications showed seven clusters. Among these, the four biggest clusters were (i) the cluster (red) on Stanford University and University of Pittsburgh; (ii) the cluster (green) on the Cleveland Clinic and the University of Michigan; (iii) the cluster (blue) on Yonsei University and Seoul National University; and (iv) the cluster (yellowish-green) on Yale University and the University of California (UC) San Diego.

Distribution by Author

A total of 18,247 authors accounted for all publications for gender-related medical AI in 2001–2020. Dey D, Kaouk JH, and Grossie E contributed the most, with 10 publications, followed by Slomka PJ and Kaouk J, with nine publications (**Table 3**). In terms of first-author publications, Lin E ranked first with five publications, whereas Lee BJ ranked second with four. Most of the high-ranked authors by publications were from the USA, except for two from Europe. For the high-ranked first-authors, six were from Asia, four from the USA, and two from Europe. In addition, the results of co-citation, bibliometric coupling, and co-authorship analysis were shown in **Supplementary Figure 1**.

Distribution by Topic

Table 4 shows the 10 most common WoS subject categories. Surgery ranked first, with 496 publications (15.9%), followed by Urology and Nephrology (n = 241; 7.7%), Medicine, General and Internal (n = 212; 6.8%), Neuroscience (n = 204; 6.6%), and Radiology, Nuclear Medicine and Medical Imaging (n = 172; 5.5%).

Figure 4 shows the network visualization map of keywords with a minimum occurrence of 20. Five clusters with 177 terms were obtained from the analysis: (i) a red cluster with 56 items focused on machine learning, classification, diagnosis, children, deep learning, and meta-analysis; (ii) a green cluster with 55 items focused on items focused on surgery, outcomes, robotic surgery, cancer, and management; (iii) a blue cluster with 47 items focused on risk, prediction, disease, mortality, health, artificial intelligence, and validation; (iv) a yellowish-green cluster with 13 items focused on stroke, therapy, rehabilitation, and reliability; and (v) a purple cluster with six items focused on index, guidelines, coronary artery disease, and intervention. Network visualization maps for keywords across the time periods were shown in **Supplementary Figure 2**.

Distribution by Journal

The 3,110 papers were published in 1,281 journals. **Table 5** lists the top 10 journals by the number of publications within the study period. The top 10 journals contributed 13.0% (403/3,110) of the total publications. *PLoS One* published the most articles on gender-related medical AI (n = 81; 2.6%), followed by *Surgical Endoscopy and Other Interventional Techniques* (n = 48; 1.5%), *Asian Journal of Surgery* (n = 44; 1.4%), and *Scientific Reports* (n = 43; 1.4%). Among the top 10 journals by publication number, *Surgical Endoscopy and Other Interventional Techniques* had the highest H-index (15), whereas the *Journal of Urology* had the largest number of citations per paper (55).

TABLE 1 | The 20 countries contributing the most gender-related articles in medical artificial intelligence.

Country	Total number of papers (%)	2001–2005			2006–2010			2011–2015			2016–2020			Change between first and fourth 5-year periods (%)
		N	SI	CNCI	*N*	SI	CNCI	*N*	SI	CNCI	*N*	SI	CNCI	
World		54		1.10	153		1.39	493		1.48	2,410		1.49	43.6
USA	1,377 (44.3)	19	1.02	1.26	78	1.78	1.87	220	1.41	1.86	1,059	1.81	1.79	54.7
Peoples R China	305 (9.8)	2	0.79	1.74	8	0.62	0.79	25	0.33	0.87	257	0.66	1.48	127.5
UK	241 (7.7)	3	0.74	1.55	10	0.95	1.51	30	0.75	2.24	198	1.28	2.64	65.0
Italy	211 (6.8)	8	3.85	0.47	15	2.53	2.11	33	1.41	0.89	155	1.63	1.87	18.4
South Korea	201 (6.5)	2	1.81	1.08	3	0.78	2.42	39	2.36	1.67	157	2.42	1.67	77.5
Germany	200 (6.4)	6	1.53	0.70	8	0.80	1.19	26	0.71	1.35	160	1.16	2.64	25.7
Canada	164 (5.3)	1	0.43	2.04	5	0.78	1.25	23	0.97	1.24	135	1.48	1.66	134.0
Turkey	121 (3.9)	2	3.64	4.31	9	4.14	0.35	21	2.14	0.43	89	2.20	0.96	43.5
Netherlands	106 (3.4)	2	1.67	0.28	2	0.60	1.14	8	0.61	2.69	94	1.86	3.67	46.0
India	101 (3.2)	2	1.96	0.58	2	0.52	1.86	9	0.40	0.90	88	0.84	1.20	43.0
Australia	94 (3.0)	–	–	–	1	0.23	0.19	13	0.64	3.15	80	0.94	2.02	–
France	91 (2.9)	2	0.75	2.01	10	1.45	1.13	16	0.64	0.86	63	0.70	2.05	30.5
Japan	88 (2.8)	3	0.74	1.19	5	0.58	0.84	16	0.59	1.00	64	0.65	0.94	20.3
Spain	85 (2.7)	2	1.37	0.48	3	0.60	1.57	11	0.53	0.90	69	0.84	1.44	33.5
Taiwan	74 (2.4)	3	4.31	0.17	4	1.69	0.60	10	1.15	1.23	57	2.01	1.35	18.0
Brazil	65 (2.1)	1	1.27	0.31	–	–	–	12	0.85	1.87	52	0.84	1.52	51.0
Iran	62 (2.0)	2	11.79	0.81	3	2.27	0.52	10	1.17	1.64	47	1.10	0.95	22.5
Switzerland	62 (2.0)	–	–	–	2	0.85	1.46	7	0.72	1.51	53	1.34	2.29	–
Sweden	56 (1.8)	–	–	–	1	0.49	3.38	11	1.32	2.34	44	1.30	2.07	–
Belgium	52 (1.7)	–	–	–	6	3.31	1.74	9	1.24	1.51	37	1.31	4.11	–

CNCI, Category Normalized Citation Impact; N, number; SI, Specialization Index; Peoples R China, People's Republic of China; UK, United Kingdom; USA, United States of America.

TABLE 2 | The institutions contributing the most gender-related articles in medical artificial intelligence.

Rank	Institution	Frequency	%	Country
1	Harvard University	142	4.6	USA
2	University of California System	136	4.4	USA
3	University of Texas System	84	2.7	USA
3	Harvard Medical School	84	2.7	USA
5	University of London	81	2.6	UK
6	US Department of Veterans Affairs	65	2.1	USA
6	Pennsylvania Commonwealth System of Higher Education Pcshe	64	2.1	USA
8	Veterans Health Administration	59	1.9	USA
9	Stanford University	55	1.8	USA
10	Cleveland Clinic Foundation	54	1.7	USA

UK, United Kingdom; USA, United States of America.

Characteristics of Top 9 Papers Most Frequently Cited

There were 44,711 citations in 3,110 publications. **Table 6** shows the top 9 papers with the highest citation frequency. The top 9 papers accounted for 7.0 % (3,112/44,711) of the total citations and were cited 346 times, on average. The work of Wynants et al. (21) was the most cited paper ($n = 567$; 1.3%), followed by the study by Poplin et al. (22) ($n = 382$; 0.9%) and Aarts et al. (23) ($n = 369$; 0.8%). Among the top 9 papers, three were published in journals with an impact factor (IF) > 20, one in a journal with an IF between 10 and 20, three in journals with IFs between 5 and 10, and two in journals with an IF < 5.

DISCUSSION

Our bibliometric analysis of the gender-related articles in medical AI revealed major changes over the last 20 years. The number of publications and percentage of gender-related articles in medical AI fields continuously increased from 2001 to 2020, with a steep increase in the past 5 years. This change can be explained by

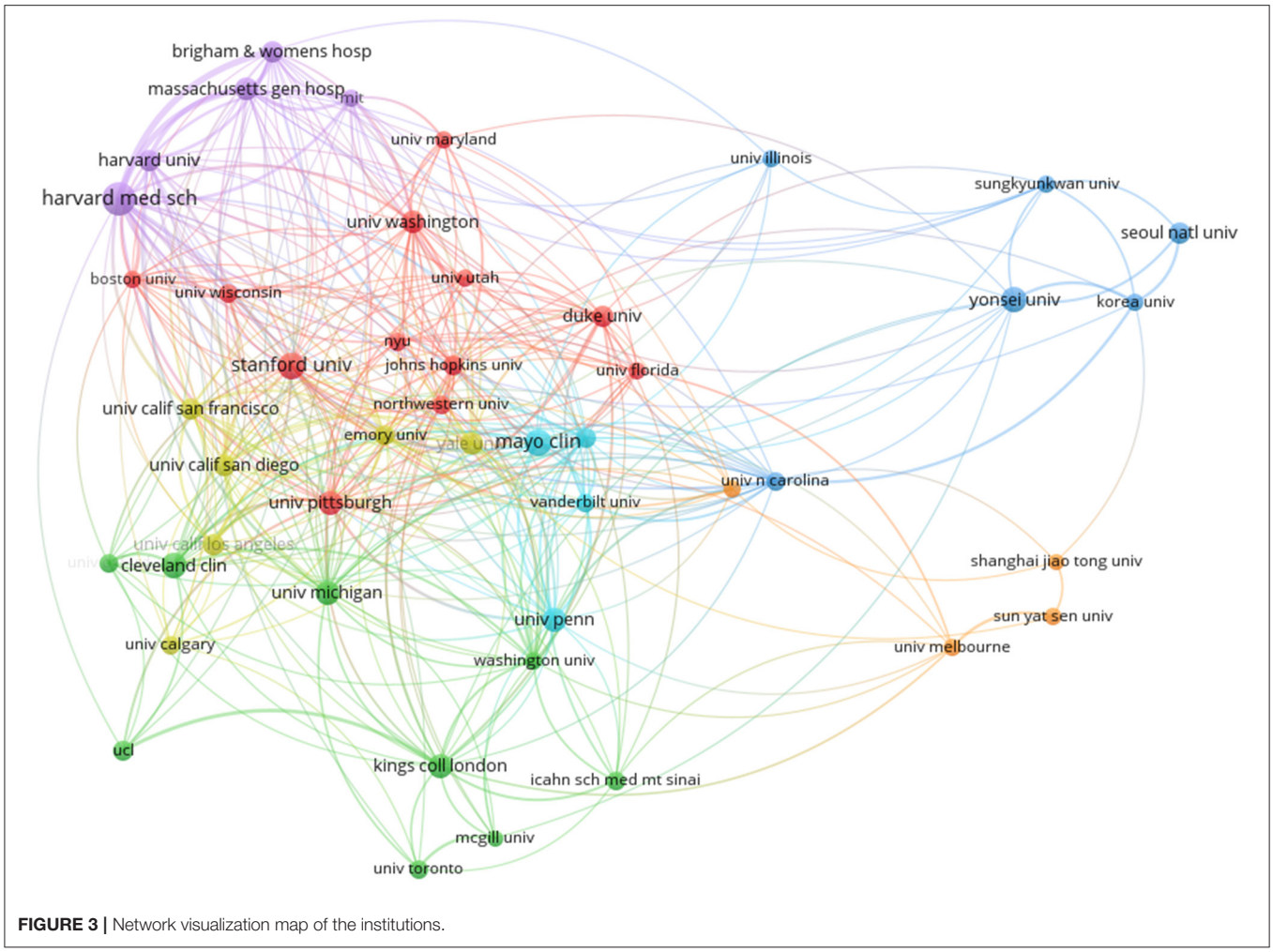


FIGURE 3 | Network visualization map of the institutions.

both increased interest of AI and awareness of gender medicine. Due to the technological development including computing power and data storage, AI has been developed (24), leading to advances in researches and collaborative works in medical AI fields (15, 25). In addition, there have been continuous efforts to overcome this gender bias (4), although women used to be underrepresented in clinical research (26).

After the National Institute of Health (NIH) Revitalization Act of 1993 mandated the enrollment of women and ethnic minorities in clinical research in the USA (27), funding agencies such as the Canadian Institutes of Health Research (28), European Commission (29), and NIH (30) required consideration of sex and gender in study design, analysis, and reporting for grant applications. In addition, several editorial guidelines included gender-specific work [e.g., Animal Research: Reporting In Vivo Experiments (ARRIVE) (31), Sex and Gender Equity in Research (SAGER) (32), and International Committee of Medical Journal Editors (ICMJE) recommendations (33)].

Both the number of publications and RRI on gender-related medical AI have steadily increased for 20 years, showing the increase of research interests in related fields. The percentage of gender-related articles in medical AI doubled in the last 20 years to 6.5%, although this figure remains small. According to Sugimoto et al., in 2016, two-thirds of articles were gender-related reporting articles of clinical medicine and public health research, whereas one-third of such articles were for biomedical research (34). Geller et al. showed that 26% of NIH-funded randomized control trials in 2018 included sex as a covariate (35). Compared to other fields, medical AI had a low percentage of gender-related articles. This requires further study.

As the number of publications can only provide volumetric information, our analysis showed SI and CNCI across countries and over time. These two parameters can provide different perspectives on research trends (36). SI, the ratio of the percentage of publications related to the specific area in a given country to those worldwide, evaluates specialization. CNCI, which is the ratio of the observed to the expected number of citations in the same WoS category, shows the citation impact. For example, although Canada and Peoples R China had the highest percentage increase in the number of publications over the previous 20 years, Canada showed overspecialization

TABLE 3 | The authors and first-authors contributing the most gender-related articles in medical artificial intelligence.

Rank	Authors	Number of papers	Affiliation	Country
High-ranked authors				
1	Dey, Damini	10	Cedars-Sinai Medical Center	USA
1	Kaouk, Jihad H.	10	Glickman Urological Institute	USA
1	Grossi, Enzo	10	Semeion Center	Italy
4	Slomka, Piotr J.	9	Department of Imaging and Medicine and the Smidt Heart Institute	USA
4	Kaouk, Jihad	9	Cleveland Clin, Glickman Urol and Kidney Inst	USA
6	Berman, Daniel S.	8	Smidt Heart Institute and Biomedical Imaging Research Institute	USA
6	Stewart, Robert	8	South London and Maudsley NHS Foundation Trust	UK
8	Schoepf, U. Joseph	7	Medical University of South Carolina	USA
8	Garisto, Juan	7	Glickman Urological and Kidney Institute	USA
High-ranked first authors				
1	Lin, Eugene	5	Vita Genomics Incorporated	Taiwan
2	Lee, Bum Ju	4	Korea Institute of Oriental Medicine	South Korea
3	Baumann, Stefan	3	University Medical Centre Mannheim	Germany
3	Choi, Ahnryul	3	Catholic Kwandong University	South Korea
3	Kandil, Emad	3	Tulane University School of Medicine	USA
3	Kang, Jeonghyun	3	Yonsei University College of Medicine	South Korea
3	Koutsouleris, Nikolaos	3	Ludwig-Maximilian-University	Germany
3	Liu, Xun	3	The Third Affiliated Hospital of Sun Yat-sen University	Peoples R China
3	Lo-Ciganic, Wei-Hsuan	3	University of Florida	USA
3	Maurice, Matthew J.	3	Cleveland Clinic	USA
3	Shiao, S. Pamela K.	3	Augusta University	USA
3	Yuvaraj, R.	3	University Malaysia Perlis	Malaysia

Peoples R China, People's Republic of China; UK, United Kingdom; USA, United States of America.

TABLE 4 | The most productive Web of Science subject categories in gender-related articles in medical artificial intelligence.

Rank	Web of Science subject category	Frequency	%
1	Surgery	496	15.9
2	Urology and Nephrology	241	7.7
3	Medicine, General and Internal	212	6.8
4	Neurosciences	204	6.6
5	Radiology, Nuclear Medicine and Medical Imaging	172	5.5
6	Medical Informatics	168	5.4
7	Clinical Neurology	160	5.1
8	Multidisciplinary Sciences	156	5.0
8	Oncology	155	5.0
10	Engineering, Biomedical	145	4.7

and citation impact specifically in gender-related medicine AI research compared to the worldwide figures, whereas Peoples R China did not.

The USA had the most publications on gender-related medical AI between 2001 and 2020, with overall high CNCIs and SIs. As expected, the top 10 institutions and high-ranked authors were from the USA. According to the network visualization plot, most of the top 10 institutions were also well-connected through research networks. According to the bibliographic analysis of authors, it was possible to understand the relationships between authors. Author co-citation analysis visualized the intellectual structure of the scientific knowledge domain by calculating how often the author's work is cited with other authors (37), whereas bibliographic coupling showed the similarity relationships by calculating how often two papers are cited together (38). In addition, co-authorship analysis showed the cooperative and interactive relationships between authors, indicating the authors' willingness to write a paper together (39).

Surgery and Urology and Nephrology was the most common WoS subject category in our analysis. Similarly, *Surgical Endoscopy and Other Interventional Techniques*, *Asian Journal of Surgery, Urology,* and *Journal of Urology* were the journals that ranked high in the number of gender-related publications in medical AI. Surgery is one of the most developed areas in medical AI. AI can be applied pre-, intra-, and post-surgery, such as for preoperative risk prediction, imaging, 3D reconstruction, and robotic intervention (40, 41). As several studies reported the sex differences in prognosis after surgery (42–44), sex should be considered in AI surgery research. Urology is another area of interest in gender-related medical AI. There are anatomical, physiological, and pathophysiological urological differences between men and women (45). Hormones and metabolisms differ by sex, thereby affecting medical conditions (46). Furthermore, environmental and occupational exposures may differ by gender, which should be considered in gender medicine (47).

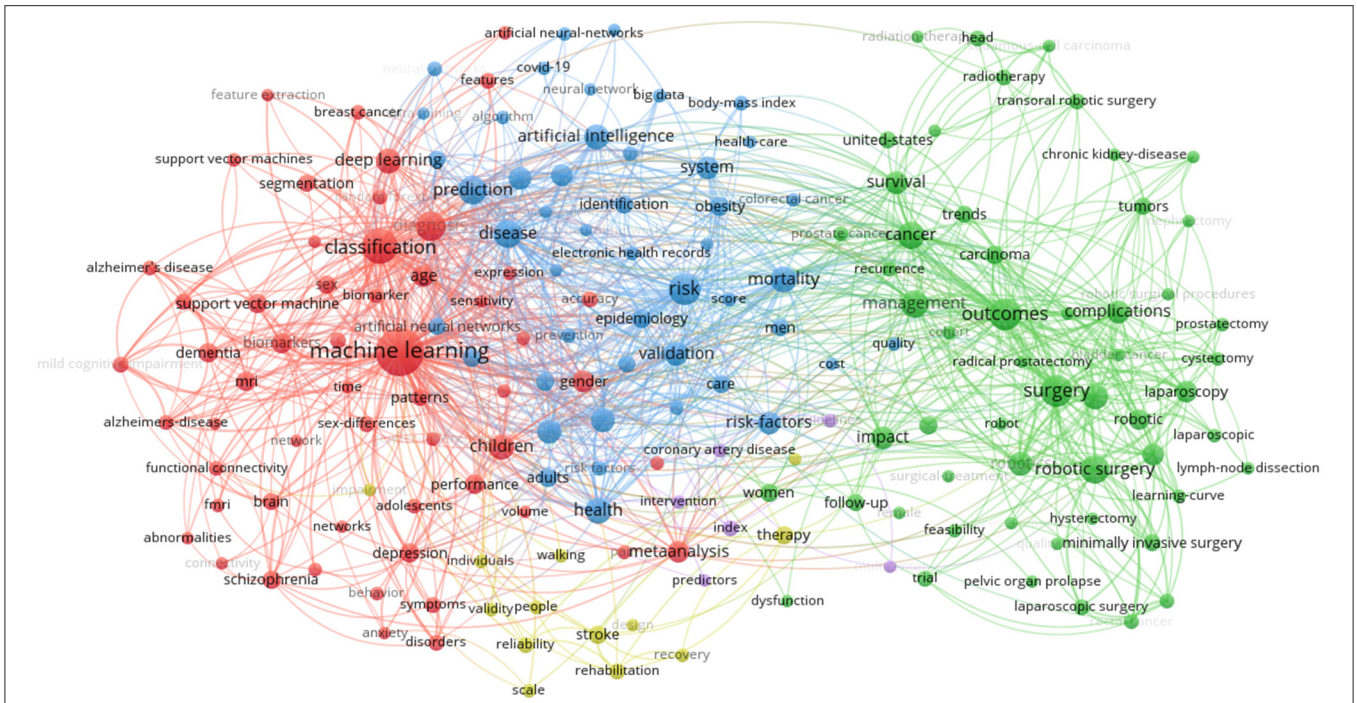


FIGURE 4 | Network visualization map of keywords. Keywords included the author's keywords and keywords plus.

TABLE 5 | The journals with the most gender-related articles in medical artificial intelligence.

Rank	Journals	Number of papers	Number of citations	Citations per paper	H-index	Impact Factor (2020)	Web of Science subject category
1	PLoS one	81	1,281	16.86	20	3.240	Multidisciplinary Sciences
2	Surgical Endoscopy and other Interventional Techniques	48	1,714	29.55	21	4.584	Surgery
3	Asian Journal of Surgery	44	242	5.5	9	2.767	Surgery
4	Scientific Reports	43	333	9	10	4.379	Multidisciplinary Sciences
5	JAMA Network Open	41	582	15.73	14	8.483	Medicine, General and Internal
5	Journal of Robotic Surgery	41	204	4.98	8	N/A	Surgery
7	Journal of Medical Internet Research	30	200	9.52	8	5.428	Health Care Sciences and Services; Medical Informatics
8	IEEE Access	28	190	6.79	6	3.367	Computer Science, Information Systems; Engineering, Electrical and Electronic; Telecommunications
9	Urology	24	374	16.26	10	2.649	Urology and Nephrology
10	Journal of Urology	23	1,320	55	16	7.450	Urology and Nephrology

N/A: not available.

The network visualization map of keywords across the time periods showed that research topics have continuously expanded and changed over past two decades. In the first period (2001–2005), there was only two clusters; one was disease and the other was artificial neural networks and cancer. In the last period (2016–2020), there was 6 clusters including machine learning, risk, and surgery. These results can be used to guide future studies by listing the trending topics.

The citation analysis showed that gender-related medical AI had a high influence, with an average of 15 citations. The topics covered in the top 9 articles with the highest citations were surgery, imaging, and prediction models. The most cited article was the study of Wynants et al. (21), which systematically reviewed and critically evaluated all 232 predictive models for diagnosis and prognosis of COVID-19 including 169 studies. This study showed that gender is one of the frequent prognostic factors of COVID-19. As the COVID-19 pandemic has posed a threat to the global economic and health systems with high morbidity and mortality (48), COVID-19-related articles have recently dominated medical publishing

TABLE 6 | The papers with the most frequent citations of gender-related medical artificial intelligence.

Rank	Title	First author	Journal	Impact factor (2020)	Year	Number of citations	Web of Science subject category
1	Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal	Wynants, Laure	BMJ-British Medical Journal	39.890	2020	567	Medicine, General and Internal
2	Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning	Poplin, Ryan	Nature Biomedical Engineering	25.671	2018	382	Engineering, Biomedical
3	Surgical approach to hysterectomy for benign gynecological disease	Aarts, Johanna W. M.	Cochrane Database of Systematic Reviews	9.266	2015	369	Medicine, General and Internal
4	Robot assisted partial nephrectomy vs. laparoscopic partial nephrectomy for renal tumors: a multi-institutional analysis of perioperative outcomes	Benway, Brian M.	Journal of Urology	7.450	2009	365	Urology and Nephrology
5	Prospective randomized controlled trial of robotic vs. open radical cystectomy for bladder cancer: perioperative and pathologic results	Nix, Jeff	European Urology	20.096	2010	362	Urology and Nephrology
6	Alzheimer's disease diagnosis in individual subjects using structural MR images: validation studies	Vemuri, Prashanthi	Neuroimage	6.556	2008	298	Neuroimaging; Neurosciences; Radiology, Nuclear Medicine and Medical Imaging
7	Transoral robotic surgery: a multicenter study to assess feasibility, safety, and surgical margins	Weinstein, Gregory S.	Laryngoscope	3.325	2012	270	Medicine, Research and Experimental; Otorhinolaryngology
8	Compare: classification of morphological patterns using adaptive regional elements	Fan, Yong	IEEE Transactions on Medical Imaging	10.048	2007	254	Computer Science, Interdisciplinary Applications; Engineering, Biomedical; Engineering, Electrical and Electronic; Imaging Science and Photographic Technology; Radiology, Nuclear Medicine and Medical Imaging
9	Robot-assisted laparoscopic pancreatic surgery: single-surgeon experience	Giulianotti, Pier Cristoforo	Surgical Endoscopy and other Interventional Technique	4.584	2010	251	Surgery

in the last 2 years (49). The study of Poplin et al., the second most cited article, developed deep learning models using retinal fundus images to predict multiple cardiovascular risk factors including age and gender (22). The third most cited article was the article by Aarts et al. (23), which reviewed the effectiveness and safety of four types of hysterectomy surgeries in women with benign gynecological diseases. Interestingly, most of the top 9 articles were published in journals with an IF $<$ 10. This demonstrates an increased interest in this field.

This bibliometric study has some limitations. First, like other bibliometric studies, the results can be affected by the search term and databases used. As we only used the WoS, we could not include publications in other electronic databases (e.g., PubMed or Embase). However, we selected the WoS covering a broad range of articles (50) and applied search strategies with high sensitivity. Second, there was a possibility of the inclusion of studies that had little to do with our topics. As we focused on showing macroscopic tendencies, studies were identified through search if they had AI-, medication-, and gender-related terms in titles, abstracts, or keywords, regardless of their topics. For example, the article by Roberts et al. (51), the originally identified as the second most cited article, suggested the structural topic models for surveys in political sciences; it was not presented in **Table 6** for qualitative interpretation. Despite this, including gender-related words is meaningful because it covers gender in any way. Third, the number of citations can be biased by self-citations and time elapsed since publication. Lastly, non-English publications were not included.

To the best of our knowledge, this is the first bibliometric study to investigate the worldwide research output of gender-related medical AI by bibliometric analysis. This study concluded that gender-related research in medical AI increased over the past 20 years. Despite increased interest, gender-related research is still low in medical AI field and further research is needed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

JY and HG contributed to designing the study. HY contributed to acquisition and analysis of data. HY, JY, and HG contributed to interpretation of data. HY and HL contributed to drafting of the manuscript. JY and HG contributed to critical revision of the manuscript. All authors contributed to the conception and design and read and approved the final manuscript.

FUNDING

The research leading to these results received funding from Ministry of Science and ICT under WISET202103GI01.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.868040/full#supplementary-material

REFERENCES

1. Baggio G, Corsini A, Floreani A, Giannini S, Zagonel V. Gender medicine: a task for the third millennium. *Clin Chem Lab Med.* (2013) 51:713–27. doi: 10.1515/cclm-2012-0849
2. Mauvais-Jarvis F, Merz NB, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, et al. Sex and gender: modifiers of health, disease, and medicine. *Lancet.* (2020) 396:565–82. doi: 10.1016/S0140-6736(20)31561-0
3. Gochfeld M. Sex differences in human and animal toxicology: toxicokinetics. *Toxicol Pathol.* (2017) 45:172–89. doi: 10.1177/0192623316677327
4. Lee SK. Sex as an important biological variable in biomedical research. *BMB Rep.* (2018) 51:167. doi: 10.5483/BMBRep.2018.51.4.034
5. Healy B. The Yentl syndrome. *N Engl J Med.* (1991) 325:274–6. doi: 10.1056/NEJM199107253250408
6. Arain FA, Kuniyoshi FH, Abdalrhim AD, Miller VM. Sex/gender medicine. The biological basis for personalized care in cardiovascular medicine. *Circ J.* (2009) 73:1774–82. doi: 10.1253/circj.CJ-09-0588
7. Freire AC, Basit AW, Choudhary R, Piong CW, Merchant HA. Does sex matter? The influence of gender on gastrointestinal physiology and drug delivery. *Int J Pharm.* (2011) 415:15–28. doi: 10.1016/j.ijpharm.2011.04.069
8. Wagner AD, Oertelt-Prigione S, Adjei A, Buclin T, Cristina V, Csajka C, et al. Gender medicine andoncology:report and consensus of an ESMO workshop. *Ann Oncol.* (2019) 30:1914–24. doi: 10.1093/annonc/mdz414
9. Safdar B, Greenberg MR. Organization, execution and evaluation of the 2014 academic emergency medicine consensus conference on gender-specific research in emergency care–an executive summary. *Acad Emerg Med.* (2014) 21:1307–17. doi: 10.1111/acem.12530
10. Rich E. Artificial intelligence and the humanities. *Comput Humanit.* (1985) 19:117–22. doi: 10.1007/BF02259633
11. Pannu A. Artificial intelligence and its application in different areas. *Artificial Intellig.* (2015) 4:79–84.
12. Mintz Y, Brodie R. Introduction to artificial intelligence in medicine. *Minim Invasive Ther Allied Technol.* (2019) 28:73–81. doi: 10.1080/13645706.2019.1575882
13. Amisha PM, Pathania M, Rathaur VK. Overview of artificial intelligence in medicine. *J Family Med Prim Care.* (2019) 8:2328–31. doi: 10.4103/jfmpc.jfmpc_440_19
14. Hamet P, Tremblay J. Artificial intelligence in medicine. *Metabolism.* (2017) 69:S36–40. doi: 10.1016/j.metabol.2017.01.011
15. Guo Y, Hao Z, Zhao S, Gong J, Yang F. Artificial intelligence in health care: bibliometric analysis. *J Med Internet Res.* (2020) 22:e18228. doi: 10.2196/18228
16. Clarivate Analytics. *Web of Science Core Collection*. (2022). Available online at: https://clarivate.com/webofsciencegroup/solutions/web-of-science-core-collection. (accessed April 5, 2022).
17. Li K, Rollins J, Yan E. Web of Science use in published research and review papers 1997-2017: a selective, dynamic, cross-domain, content-based analysis. *Scientometrics.* (2018) 115:1–20. doi: 10.1007/s11192-017-2622-5
18. Meho LI, Yang K. Impact of data sources on citation counts and rankings of LIS faculty: Web of science versus scopus and google scholar. *J Am Soc Inf Sci Technol.* (2007) 58:2105–25. doi: 10.1002/asi.20677
19. UNESCO Institute for Statistics. *What Do Bibliometric Indicators Tell Us About World Scientific Output*? UIS Bulletin on Science and Technology Statistics (2005). p. 1–6.
20. Normalized Indicators (2020). Available online at: https://incites.help.clarivate.com/Content/Indicators-Handbook/ih-normalized-indicators.htm# (accessed April 5, 2022).
21. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ.* (2020) 369:m1328. doi: 10.1136/bmj.m1328
22. Poplin R, Varadarajan AV, Blumer K, Liu Y, McConnell MV, Corrado GS, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng.* (2018) 2:158–64. doi: 10.1038/s41551-018-0195-0
23. Aarts JW, Nieboer TE, Johnson N, Tavender E, Garry R, Mol BWJ, et al. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev.* (2015) 2015:CD003677. doi: 10.1002/14651858.CD003677.pub5
24. Tipol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med.* (2019) 25:44–56. doi: 10.1038/s41591-018-0300-7
25. Ho YS, Wang MH. A bibliometric analysis of artificial intelligence publications from 1991 to 2018. *COLLNET J Scientometr Inform Manag.* (2020) 14:369–92. doi: 10.1080/09737766.2021.1918032
26. Vidaver RM, Lafleur B, Tong C, Bradshaw R, Marts SA. Women subjects in NIH-funded clinical research literature: lack of progress in both representation and analysis by sex. *J Womens Health Gender Based Med.* (2000) 9:495–504. doi: 10.1089/15246090050073576
27. National Institutes of Health. *NIH Revitalization Act of 1993. Public Law.* (1993). p. 103–43.
28. Johnson JL, Beaudet A. Sex and gender reporting in health research: why Canada should be a leader. *Can J Public Health.* (2013) 104:e80–81. doi: 10.1007/BF03405660
29. European Commission. *Fact Sheet: Gender Equality in Horizon 2020.* (2013). Available online at: https://ec.europa.eu/programmes/horizon2020/sites/default/files/FactSheet_Gender_2.pdf
30. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature News.* (2014) 509:282–3. doi: 10.1038/509282a
31. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biol.* (2010) 8:e1000412. doi: 10.1371/journal.pbio.1000412
32. De Castro P, Heidari S, Babor TF. Sex and gender equity in research (SAGER): reporting guidelines as a framework of innovation for an equitable approach to gender medicine. *Ann Ist Super Sanita.* (2016) 52:154–57. doi: 10.4415/ANN_16_02_05
33. International Committee of Medical Journal Editors (ICMJE). *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*. (2019). Available online at: www.icmje.org/icmje-recommendations.pdf

34. Sugimoto CR, Ahn YY, Smith E, Macaluso B, Larivière V. Factors affecting sex-related reporting in medical research: a cross-disciplinary bibliometric analysis. *Lancet.* (2019) 393:550–59. doi: 10.1016/S0140-6736(18)32995-7
35. Geller SE, Koch AR, Roesch P, Filut A, Hallgren E, Carnes M. The more things change, the more they stay the same: a study to evaluate compliance with inclusion and assessment of women and minorities in randomized controlled trials. *Acad Med.* (2018) 93:630. doi: 10.1097/ACM.0000000000002027
36. Devos P, Ménard J. Trends in worldwide research in hypertension over the period 1999–2018: a bibliometric study. *Hypertension.* (2020) 76:1649–55. doi: 10.1161/HYPERTENSIONAHA.120.15711
37. Bayer AE, Smart JC, McLaughlin GW. Mapping intellectual structure of a scientific subfield through author cocitations. *J Am Soc Inform Sci.* (1990) 41:444.
38. Zhao D, Strotmann A. Evolution of research activities and intellectual influences in information science 1996–2005: introducing author bibliographic-coupling analysis. *J Am Soc Inform Sci Technol.* (2008) 59:2070–86. doi: 10.1002/asi.20910
39. Huang MH, Chang YW. A study of interdisciplinarity in information science: using direct citation and co-authorship analysis. *J Inform Sci.* (2011) 37:369–78. doi: 10.1177/0165551511407141
40. Hashimoto DA, Ward TM, Meireles OR. The role of artificial intelligence in surgery. *Adv Surg.* (2020) 54:89–101. doi: 10.1016/j.yasu.2020.05.010
41. Zhou XY, Guo Y, Shen M, Yang GZ. Application of artificial intelligence in surgery. *Front Med.* (2020) 14:1–7. doi: 10.1007/s11684-019-0733-5
42. Hogue CW Jr, Barzilai B, Pieper KS, Coombs LP, DeLong ER, Kouchoukos NT, et al. Sex differences in neurological outcomes and mortality after cardiac surgery: a society of thoracic surgery national database report. *Circulation.* (2001) 103:2133–7. doi: 10.1161/01.CIR.103.17.2133
43. de Perrot M, Licker M, Bouchardy C, Usel M, Robert J, Spiliopoulos A. Sex differences in presentation, management, and prognosis of patients with non–small cell lung carcinoma. *J Thorac Cardiovasc Surg.* (2000) 119:21–6. doi: 10.1016/S0022-5223(00)70213-3
44. Tighe PJ, Riley III JL, Fillingim RB. Sex differences in the incidence of severe pain events following surgery: a review of 333,000 pain scores. *Pain Med.* (2014) 15:1390–404. doi: 10.1111/pme.12498
45. Abelson B, Sun D, Que L, Nebel RA, Baker D, Popiel P, et al. Sex differences in lower urinary tract biologyand physiology. *Biol Sex Differ.* (2018) 9:1–13. doi: 10.1186/s13293-018-0204-8
46. Moon JY, Choi MH, Kim J. Metabolic profiling of cholesterol and sex steroid hormones to monitor urological diseases. *Endocr Relat Cancer.* (2016) 23:R455–67. doi: 10.1530/ERC-16-0285
47. Fajkovic H. Editorial comment: gender medicine in urology. *Curr Opin Urol.* (2019) 29:247–8. doi: 10.1097/MOU.0000000000000597
48. World Health Organization (WHO). *Coronavirus Disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update*. (2022). Available online at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. (accessed April 5, 2022).
49. Kousha K, Thelwall M. Covid-19 refereeing duration and impact in major medical journals. *Quan Sci Stud.* (2022) 3:1–17. doi: 10.1162/qss_a_00176
50. Yang K, Meho LI. Citation analysis: a comparison of Google Scholar, Scopus, and Web of Science. *Proc Am Soc Inform Sci Technol.* (2006) 43:1–15. doi: 10.1002/meet.14504301185
51. Roberts ME, Stewart BM, Tingley D, Lucas C, Leder-Luis J, Gadarian SK, et al. Structural topic models for open-ended survey responses. *Am J Pol Sci.* (2014) 58:1064–82. doi: 10.1111/ajps.12103

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 31 October 2022
DOI 10.3389/fmed.2022.1009432

OPEN ACCESS

EDITED BY
Mette Due Theilade Thomsen,
PIP Adviser, Denmark

REVIEWED BY
Gesine Bejeuhr,
Bayer, Germany
Christina Bucci-Rechtweg,
Novartis, United States

*CORRESPONDENCE
Helle Christiansen
hchristiansen@sund.ku.dk

SPECIALTY SECTION
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

RECEIVED 01 August 2022
ACCEPTED 17 October 2022
PUBLISHED 31 October 2022

CITATION
Christiansen H, De Bruin ML and Hallgreen CE (2022) Mandatory requirements for pediatric drug development in the EU and the US for novel drugs—A comparative study. *Front. Med.* 9:1009432. doi: 10.3389/fmed.2022.1009432

Mandatory requirements for pediatric drug development in the EU and the US for novel drugs—A comparative study

Helle Christiansen[1]*, Marie L. De Bruin[1,2] and Christine E. Hallgreen[1]

[1]Copenhagen Centre for Regulatory Science, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [2]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands

Mandatory pediatric legislation has been implemented in the European Union (EU) and the United States (US) to increase research and the availability of drugs for the pediatric population. Differences in the legislative framework can cause different pediatric requirements for similar indications granted for similar drugs across jurisdictions. This cross-sectional study compares the pediatric requirements for therapeutic indications granted at the time of initial approval for novel drugs approved in the two regions from 2010 to 2018. We collected the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) decisions to grant a waiver and/or to agree on a pediatric development plan and deferrals hereof at marketing authorization (MA) from publicly available documents. An agreed pediatric development plan was required for 66% (N = 188/285) and 63% (N = 134/212) of the indications granted in the EU and the US at the time of approval, respectively. Almost all (EU; 98%, US; 89%) were deferred until after MA. Based on the broad scope of the EU Pediatric Regulation, an additional 36 PIPs originated from the indications granted at MA. In the subset of indications granted for drugs approved in both the EU and the US (N = 232), significantly more indications resulted in an agreed pediatric development plan for one or more subsets of the pediatric population in the EU (N = 185) as compared to the US (N = 82). This was based on the exemption of orphan designated drugs in the US and the broader scope of the EU Pediatric Regulation. However, indications subject to the mandatory pediatric legislation in both regions (N = 131) most often had similar regulatory requirements for the inclusion of the pediatric population from the EMA and the US FDA (83%, N = 109). In conclusion, when comparing mandatory pediatric requirements, more pediatric development plans were agreed upon in the EU than in the US, in line with the broader mandates of the EU Pediatric Regulation. However, authorities most often had similar regulatory requirements when an indication was subject to pediatric legislation in both regions.

KEYWORDS

EU Pediatric Regulation, Pediatric Research Equity Act, legislation, pediatric drug development, EMA, FDA

Introduction

In the past, medicinal products were rarely evaluated in the pediatric population, resulting in a scarcity of drugs approved for use in the pediatric population, resulting in a high level of off-label use in this population. Since market forces have not been able to drive changes, initiatives have been implemented in several regulatory regions to support the establishment of knowledge on how to use medicinal products in the pediatric population (1). However, the European Union (EU) and the United States (US) were the first regions to introduce mandatory pediatric legislations (2, 3).

The US Pediatric Research Equity Act (PREA) made the inclusion of the pediatric population (from birth to the age of 16 years) mandatory during drug development when it came into force in December 2003 (3). It complemented the already existing voluntary Best Pharmaceuticals for Children Act (BPCA) implemented in 2002 (4) where a reward could be gained for the conduct of requested pediatric drug development. The EU Pediatric Regulation adopted in December 2006 was built upon the learnings from the US (2) and combined mandatory requirements with rewards as incentives for pediatric drug development.

Except for orphan drugs which are exempted from US PREA but not the EU Pediatric Regulation, the overall framework is quite similar across the two jurisdictions; both the US PREA and the EU Pediatric Regulation mandate submission of results from clinical studies that included the pediatric population specified in an agreed pediatric development plan (Pediatric Study Plan (PSP) in the US and Pediatric Investigation Plan (PIP) in the EU) before a marketing authorization (MA) application is considered valid unless requirements for pediatric development have been waived or deferred until after MA. Thus, if appropriate measures are not taken to include the pediatric population during the drug development of novel drugs or already approved drugs still covered by a patent or a supplementary protection certificate, entry to the market can be blocked in the EU and the US.

Besides the exemption of orphan drugs in the US PREA, also the broader scope of the mandatory EU Pediatric Regulation compared to the US PREA has been highlighted as a major difference between the two legislations, and so have the broader options/reasons for granting a waiver by US FDA compared to EMA (5). These differences can potentially lead to regional differences in the decisions on the requirements for the inclusion of the pediatric population during drug development. Such regional regulatory differences can have practical implications for applicants when running a global drug development program, which is critical to the conduct of effective, efficient, and ethical drug development for small populations, such as the pediatric population (6).

First, a difference in regulatory requirements can arise from the scope since the US PREA is restricted to the proposed indication(s) for the adult population, whereas the EU Pediatric Regulation provides a mandate for the European Medicines Agency (EMA) to require a drug development for the pediatric population for another indication *within* the condition of the proposed indication if a potential pediatric need exist (7). Therefore, a PIP can cover an indication not intended by the applicant and therefore not granted at the initial MA, but only targeted in a PIP. In this way, potential pediatric use outside the proposed adult indication cannot be ignored. Second, a difference in regulatory requirements can arise from a difference in the grounds for granting waivers. The reasons for granting a waiver are more or less the same between the EU and the US, with one exception. In the US, a waiver can be granted based on the ground that the necessary studies are impossible or highly impracticable (e.g., because the patients are geographically dispersed), but this is not the case in the EU.

In 2007, a pediatric cluster was established between the EMA and the US Food and Drug Administration (FDA) with the objective of avoiding the exposure of children to unnecessary trials and facilitating global pediatric development plans based on scientific grounds, and compatible with both agencies' legislations (8). However, consensus cannot always be reached based on different legislations, standards of care, and cultures (9). It remains to be seen if this harmonization effort can facilitate regulatory understanding leading to similar regulatory decisions between the jurisdictions (10).

To our knowledge, only one study has benchmarked the requirements for pediatric drug development between the EU and the US. This study investigated the EMA decisions for waiver applications in the EU in relation to the US FDA, showing a high similarity in decisions (13). However, the study did not give a complete overview of decisions in both regions, and it did not cover decisions for agreed pediatric development plans (PIPs or PSPs).

This study aims to provide a complete overview of the decisions by the EMA and the FDA to grant a waiver and/or to agree on a pediatric development plan (PIP or PSP) for indications granted at the initial time of MA for novel drugs approved in the EU and the US between 2010 and 2018. In addition, we analyze the concordance of regulatory decisions on the indications to be studied under a pediatric development plan for indications authorized in both regions. For this subset, we provide details on requirements for pediatric development plans for indications only subject to the EU Pediatric Regulation, but outside the scope of US PREA.

Methods

Study design

We performed a retrospective cross-sectional analysis of the decisions by the EMA and the FDA on the granting of waivers or the agreement of pediatric development plans (PIP or PSP)

for indications at the time of the first MA for all novel drugs approved in the EU through the centralized procedure or in the US between 1 January 2010 and 31 December 2018. Novel drugs were identified using a list of New Active Substances (NAS) authorized in the US, and/or in the EU maintained by the CIRS (Center for Innovation in Regulatory Science) (14, 15) for research purposes (see Supplementary material for CIRS definition of NAS).

Data sources

For all drugs approved in the US, the US letters and authorization information were retrieved from the FDA website, FDA's CDER (16) or CBER (17). For drugs approved in the EU, EPARs (European Public Assessment Reports) were retrieved from the EMA website and authorization information was collected from the so-called "download list" of all EPARs for human and veterinary medicines (18). The EMA decision number valid at the time of MA was identified using the EPAR section "1.1.2. Information on pediatric requirements". This number (P/XXXX/YEAR, e.g., P/0297/2013 for Alirocumab) was used to identify the EMA decision on the agreement of pediatric investigation plans and the granting of deferrals and waivers[1] *via* a google search. If the decision could not be found, the information was requested through the EMA access-to-documents request (19).

Data collection

For each product, we extracted the approval date, therapeutic area [Anatomical Therapeutic Chemical (ATC) Classification based on international non-proprietary name (INN)], and orphan status in the respective region. The ATC classification was used as a starting point to match identical drugs approved in both regions, followed by manual quality checks, e.g., to assign drug pairs for further analysis in case of multiple potential matches.

For each unique ATC, the EPARs and the US letters were scrutinized to collect all indications granted at initial MA (adult and pediatric) to create the study unit of drug-indication (from now on just called indications). In addition, all EMA decisions on waivers or agreed PIPs were scrutinized to collect additional indications only targeted in a PIP (from now on referred to as "indications only targeted in a PIP"). All indications were recorded at the level of condition or disease (depending on the details in the documents) using the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) (20).

For each authorized indication or indication only targeted in a PIP, the corresponding decisions by the EMA and the FDA on granting a waiver or agreement on a pediatric development plan (PIP or PSP) were collected (from now on "requirements for a pediatric development plan"). The requirements for a pediatric development plan were categorized as either a "full waiver" (a waiver covering all subsets of the pediatric population), a "partial pediatric development plan" (an agreed pediatric development plan (PIP or PSP) with a waiver for one or more subsets of the pediatric population) or a "full pediatric development plan" (an agreed pediatric development plan (PIP or PSP) for the entire pediatric population). Information on deferral for one or more subsets of a partial or full pediatric development plan was also collected, as were the reasons for granting a waiver. The pediatric subgroups (adolescent, children, toddler and infants, and term newborn) were defined by the International Conference on Harmonization (ICH) Topic E 11, 2001 (21).

Data analysis

For each region, we reported on granted waivers and agreed pediatric development plans (full or partial) with deferrals hereof in absolute numbers and percentages for all approved indications, and stratified by therapeutic area. Therapeutic areas were defined according to the primary System Organ Class (SOC) of the MedDRA (20) covered by each indication. Further, we reported on the reasons for granting waivers in each region. In addition, we provided an overview of the concordance between the decisions by the EMA and FDA on granting waivers and/or agreement of pediatric development plans for indications granted for drugs approved in both the EU and the US. Further, for each pediatric subgroup, we tested if there was a difference in requirements for pediatric development in EU and US, using χ^2 test of independence. All calculations were performed using statistical software R, version 3.6.0 (2019-04-26) (22).

Results

Characteristics of study sample

From 2010 to 2018, 255 drugs were approved in the EU through the centralized procedure as novel therapeutics, comprising 285 indications at MA (Figure 1). In the same period, the FDA approved 343 drugs as novel therapeutics, comprising 371 indications. All 285 indications granted in the EU were subject to the EU Pediatric Regulation. In addition, we observed additional 52 indications only targeted in a PIP originating from the approved indications at MA. In the US, only 212 indications were subject to the US PREA since 159 indications were granted an orphan drug designation exempting them from mandatory pediatric requirements.

1 Opinion of the Pediatric Committee on the agreement of a Pediatric Investigation Plan and a deferral and a waiver.

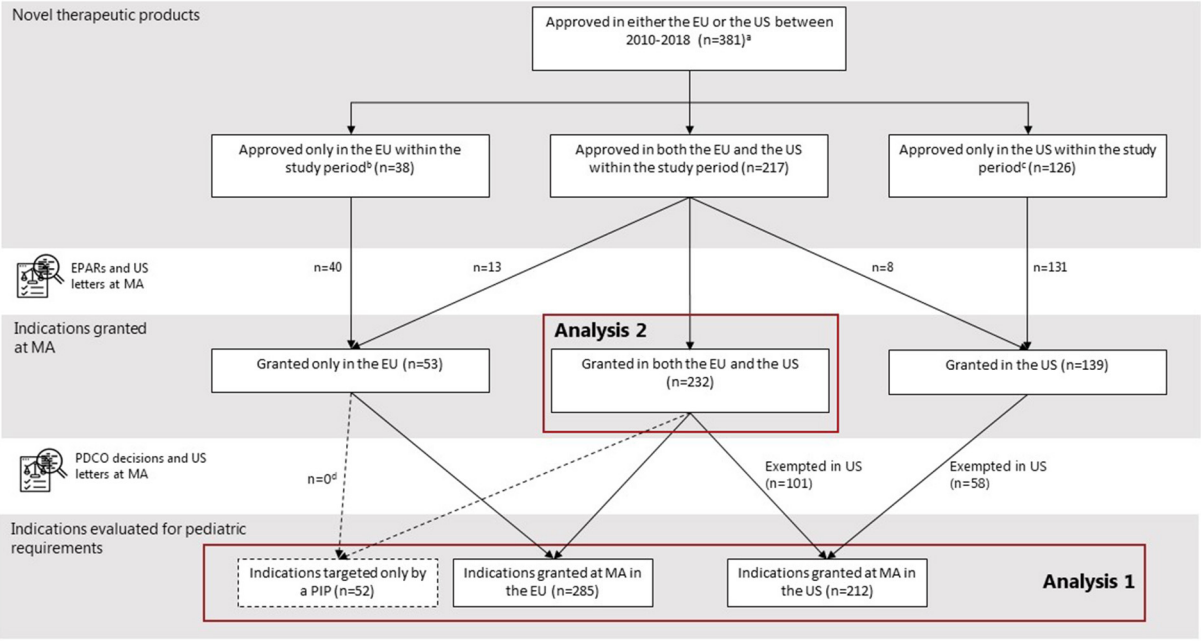


FIGURE 1
Selection of study cohort. [a]Two NAS were excluded because they were not defined as a NAS by the EMA and the US. [b]In the US, some drugs were approved before ($N = 12$) or after the ($N = 4$) study period, not considered novel at initial MA ($N = 5$), or not approved ($N = 17$). [c]In the EU, some drugs were approved before ($N = 18$) or after ($N = 22$) study period, not considered novel at initial MA ($N = 8$), not approved through the centralized procedure ($N = 4$), or not approved ($N = 74$). [d]None of the indications targeted only by a PIP originated from the indications granted only in the EU at time of MA.

Mandatory pediatric requirements in the EU and the US

The majority of the indications granted at MA and being subject to the EU Pediatric Regulation or the US PREA (EU: 66%, 188/285, US: 63%, 134/212), had a partial (EU; $N = 114$, US; $N = 100$) or full (EU; $N = 74$, US; $N = 34$) pediatric development plan (see Table 1). However, almost all (EU; 98%, $N = 185/188$, US; 89%, $N = 119/134$) were deferred for at least one measure until after MA. In the US, pediatric development plans had been completed at MA for 15 indications covering 15 drugs (for details see Supplementary Table S2). In the EU, this was the case for three indications granted for three different drugs.

Pediatric requirements were not always mandated for the 52 indications only targeted in a PIP as 16 were granted a waiver. None of the 36 agreed pediatric development plans (full: $N = 9$, partial: $N = 27$) had been completed at the time of MA, all were granted a deferral.

For all indication, partial pediatric development plans most often only included adolescents and to some extend children, and the youngest age groups were rarely covered. Only one indication (neonatal seizure) had a pediatric plan covering term newborns (neonates) (see Table 1).

Waiver reasons

In the US, most waivers (87%, full waivers: $N = 72/78$, waivers granted for a subset of the pediatric population: $N = 83/100$) were granted because necessary studies would be impossible or highly impracticable (Table 2). Whereas in the EU, waivers most often (65%, full waivers $N = 43/133$ and waivers granted for a subset of the pediatric population $N = 122/141$) were justified based on no significant therapeutic benefit in the pediatric population or the presence of a low number of pediatric patients for the given indication. In both regions, only few waivers were granted based on safety issues.

Therapeutic areas of waivers and pediatric development plans

The top three most common therapeutic areas evaluated for pediatric requirements in both jurisdictions consisted of cancer, infections/infestations, and inherited disorders (Figures 2, 3). However, in the US, a PSP was agreed for only a minority of the indications within the field of inherited disorders and cancer as these indications often were granted a waiver. In the EU, a bit less than half of the indications evaluated for pediatric requirements within the field of cancer were waived,

TABLE 1 Granted waivers and agreed pediatric development plans (PIP or PSP) for novel drug indications granted at MA between 2010 and 2018 - US ($N = 371$) and EU ($N = 285$).

	US		EU			
			Indications granted at MA		Indications only targeted in a PIP	
	No.	(%)	No.	(%)	No.	(%)
Number of indications evaluated for pediatric requirements	212[a]	(100%)	285	(100%)	52	(100%)
Number of indications granted a full waiver	78	(37%)	97	(34%)	16	(31%)
Number of indications with a full pediatric development plan	34	(16%)	74	(26%)	9	(17%)
- Of which deferred until after MA[b]	27	(13%)	72	(25%)	9	(17%)
Number of indications with a partial pediatric development plan	100	(47%)	114	(40%)	27	(52%)
- Of which deferred until after MA[b]	92	(43%)	113	(40%)	27	(52%)
Age categories covered by partial pediatric development plans						
- Adolescents (12–18 years[c])[d]	100	(47%)	114	(40%)	26	(50%)
- Children (2–11 years)[d]	31	(15%)	44	(15%)	20	(38%)
- Toddlers and infants (27 days-23 months)[d]	7	(3%)	7	(2%)	3	(6%)
- Term newborn (0–26 days)	0	(0%)	0	(0%)	1[e]	(2%)

[a]The numbers differ from the actual indications granted at the initial MA (given in the header) since 159 indications were exempted in the US due to an orphan drug designation. [b]Those not deferred had a compliance check at MA. In the US, a statement of correct indications for population or fulfillment of pediatric requirements was made. [c]12–17 years in the US. [d]Waiver can include one or more subsets of the pediatric population. [e]PIP only agreed for term newborns for the indication of neonatal seizures.

TABLE 2 Reasons for granting a full waiver or a waiver for one or more subgroups of the pediatric population for indications evaluated by the EMA PDCO (N = 337) or the US FDA (N = 212).

	EU		US	
	No.	(%)	No.	(%)
Full waiver				
Number of indications granted a full waiver	113[a]	(100%)	78[a]	(100%)
- Class waiver	58	(51%)	NA	NA
- Product-specific	55	(49%)	NA	NA
The necessary studies are impossible or highly impracticable	NA	NA	72	(92%)
Ineffective or unsafe	6	(5%)	2	(3%)
No significant therapeutic benefit OR a low number of pediatric patients	43	(38%)	2	(3%)
- The condition or disease for which the specific medicinal product or class is intended occurs only in the adult population	28	(25%)	NA	NA
- The specific medicinal product does not represent a significant therapeutic benefit over existing treatments for pediatric patients	15	(13%)	NA	NA
No reason provided[b]	64	(57%)	2	(3%)
Waiver for one or more subgroups of the pediatric population				
Number of indications with an agreed PIP for only a subset of the pediatric population	141[c]	(100%)	100[c]	(100%)
The necessary studies are impossible or highly impracticable	NA	NA	83	(83%)
Ineffective or unsafe	17	(12%)	5	(5%)
No significant therapeutic benefit OR a low number of pediatric patients	122	(87%)	9	(9%)
- The condition or disease for which the specific medicinal product or class is intended occurs only in the adult population	46	(33%)	NA	NA
- The specific medicinal product does not represent a significant therapeutic benefit over existing treatments for pediatric patients	76	(54%)	NA	NA
No reason provided	2	(1%)	3	(3%)

Percentages are calculated from the number of indications with a full waiver or the number of indications with a waiver for one or more subgroups of the pediatric population.
[a]For 34 indications a waiver was granted in both regions. [b]The most common ground for not providing a reason in the EU was indications for medicines covered by a class waiver (N = 58). Class waivers are granted to medicines that are likely unsafe or ineffective in children, lack benefit for children or are for diseases and conditions that only affect the adult population.
[c]For 57 indications a waiver was granted in both regions for one or more subgroups.

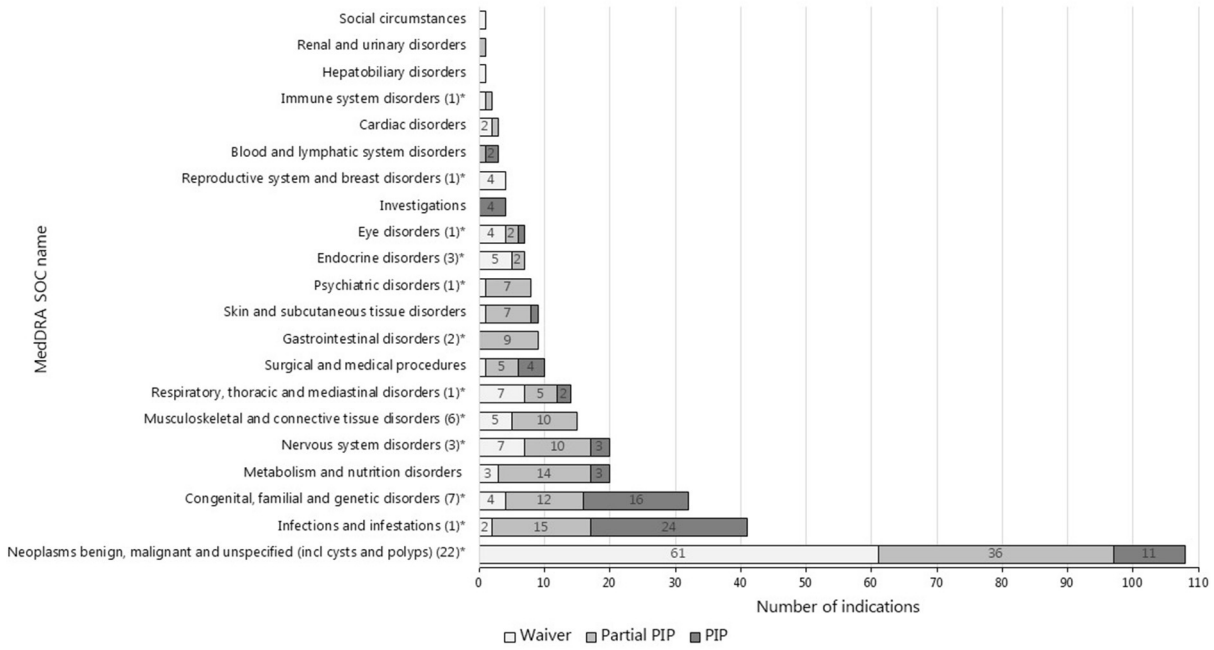


FIGURE 2
Therapeutic areas of indications evaluated for pediatric requirements in the EU ($N = 337^{\#}$). #This is the total number of indications evaluated for pediatric requirements in the EU arising from the indications approved at MA ($N = 285$) and the indications only targeted in a PIP ($N = 52$). *The number of indications targeted only by the PIP is provided in the brackets.

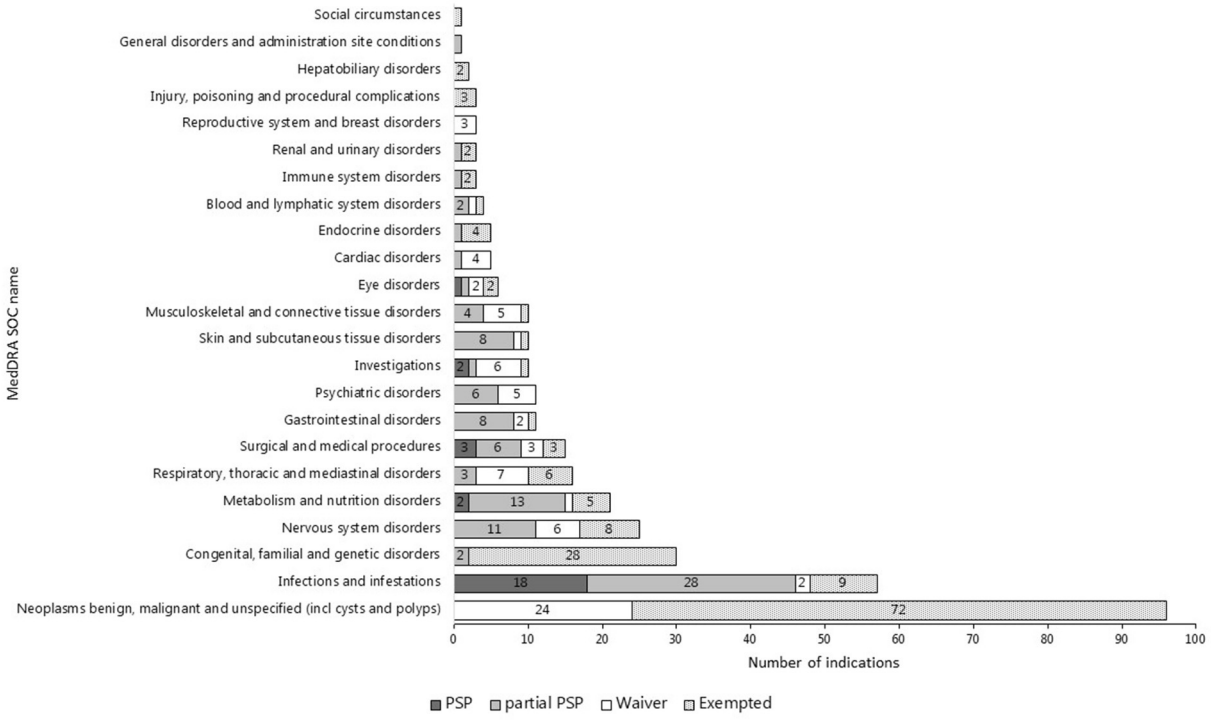


FIGURE 3
Therapeutic areas of indications evaluated for or exempted from pediatric requirements in the US ($N = 371$).

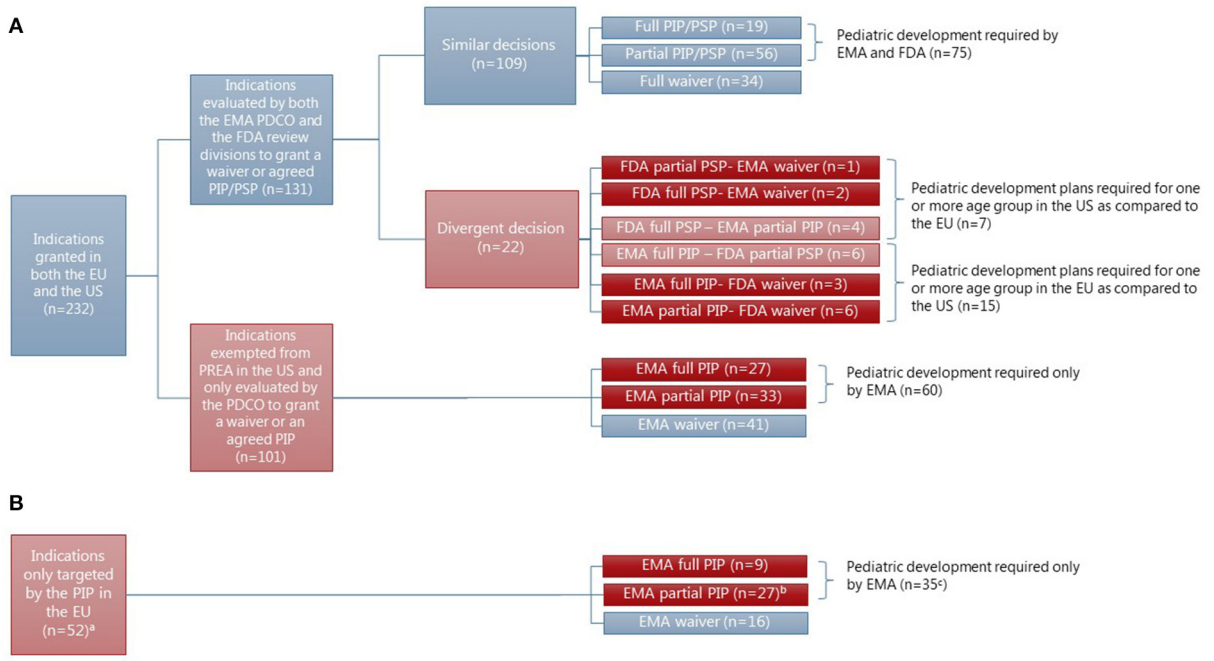


FIGURE 4
Concordance in the granting of waivers or agreement of PIP/PSP for indications granted at MA in both the EU and the US ($N = 232$) for drugs approved in both regions ($N = 217$). [a]Two indications were granted approval at MA by the FDA but not the EMA, however, they were evaluated by the EMA for granting of waiver or agreement of PIP as indications only targeted in a PIP in the EU. [b]One indication (for linaclotide-constipation) was approved in the US at MA and a pediatric development plan was agreed upon for adolescents in both the EU and the US. [c]The number does not fit since one indication (constipation) had an agreed pediatric development plan in the US as well. **(A)** Indication granted at the time of initial approval of novel drugs in the EU and the US. **(B)** Indication only targeted in a PIP.

however, most indications within inherited disorders and infections/infestations had an agreed PIP with a development plan for at least a subset of the pediatric population, but even more frequently for the entire population.

The indications only targeted in a PIP most often also covered the therapeutic area of cancer ($N = 22$) and inherited disorders ($N = 7$), but also musculoskeletal and connective tissue disorders ($N = 6$) were covered (see Figure 2).

Differences in regulatory decisions for indications *authorized* in both the EU and the US

In the subset of indications granted at MA for drugs approved in both the EU and the US and the indications only targeted in a PIP originating hereof ($N = 284$) (see Figures 4A,B), the statistical analysis showed a significant difference between the pediatric requirements mandated in the EU and the US for all the pediatric subgroups (adolescents: X-squared = 69.052, df =1, $p < 2.2e\text{-}16$, children: X-squared = 55.476, df =1, $p = 9.459e\text{-}14$, toddlers and infants: X-squared = 22.095, df =1, $p = 2.594e\text{-}06$, term newborns: X-squared = 20.082, df =1, $p = 7.419e\text{-}06$) (see Supplementary Table S6).

The majority of differences were based on indications with an orphan drug designation in the US, thereby exempting them from US PREA ($N = 101$). For 60 of these indications (see Figure 4A), a pediatric development plan was required in the EU; either for the entire pediatric population ($N = 27$), adolescents and children ($N = 20$), or only adolescents ($N = 13$). The therapeutic areas were most often covered by an agreed full or partial PIP for cancer ($N = 25$) and inherited disorders ($N = 17$). However, more than half of the indications covering cancer ($N = 29$) were granted a waiver in the EU, resulting in no pediatric development plan in either of the regions (see Supplementary Table S3). No waivers were granted in the EU for indications within the area of inherited disorders.

The remaining differences emerged from indications only targeted in a PIP in the EU, with a pediatric development plan agreed for 35 indications for at least one subset of the pediatric population as compared to the US (see Figure 4B). Two of the indications with an agreed pediatric development plan in the EU had also been evaluated for pediatric

requirements in the US, but only one resulted in a pediatric development plan.

Concordance in regulatory decisions for indications *evaluated* for pediatric requirements in both the EU and the US

In the subset of indications granted at the time of initial approval of novel drugs in the EU and the US and subject to the mandatory pediatric legislations in both the EU and the US ($N = 131$), no statistically significant difference was found between pediatric requirements mandated in the EU and the US for any of the four pediatric subgroups (see Supplementary Table S7). For these indications, the EMA and the FDA made a similar decision for the vast majority [83%, $N = 109$ (see Figure 4A)]. Even decisions on deferrals and the included age groups of a partially agreed pediatric development plan were most often similar. Of the 19 indications with an agreed pediatric development plan for the entire pediatric population, 14 were granted a deferral in both regions and four were granted only in the EU. For one indication (hemophilia A), the agreed pediatric development plan had been completed at MA in both the EU and the US (Supplementary Table S2). Of the agreed partial pediatric development plans ($N = 56$) in both the EU and the US, the included age groups only differed for four indications covering children (waiver granted in the US: $N = 2$ or EU: $N = 1$) or toddlers and infants (waiver granted in the US: $N = 1$). However, a divergent decision was made by the EMA and the FDA for 22 indications (17%) (see Figure 4), most often resulting in a pediatric development plan agreed for more subsets of the pediatric population in the EU as compared to the US ($N = 15$) (see Figure 4, for details, see Supplementary Table S5).

Discussion

Global drug development is necessary to avoid duplication of clinical trials and decrease the time to patient access, especially when developing drugs for small populations such as the pediatric population. Global development activities depend very much on an ambition to harmonize regulatory requirements around the world to enable an aligned development strategy.

This study provides an analysis of the degree of differences and similarities in regulatory requirements for pediatric drug development based on the mandatory pediatric legislations in the EU and the US for novel drugs approved in both region. Our study shows an overall significant difference in the pediatric requirements mandated by the EMA and the FDA for indications granted at MA that can be attributed to the differences between the EU Pediatric Regulation and the US PREA.

The differences seen in the regulatory requirements mainly arise from the exemption of orphan drug designated indications, which constitute a little less than half of the indications granted in both the US and the EU, most often covering cancer diseases and to a smaller extent inherited disorders. In general, it has been shown that the US FDA grants more orphan drug designations as compared to the EMA (23) and therefore, the exemption could have a rather large impact. However, a recent study with a similar study sample, found only a few discrepancies between the guidance for pediatric use in the prescription information (24), suggesting that the impact of the observed differences in requirements on the regulatory output is rather small. There could be several reasons for this. First, the pediatric drug development for orphan drugs in the US could be driven by other regulatory policies such as the US BPCA or the orphan drug legislation. The orphan drug legislation provides incentives to develop drugs to prevent, diagnose, or treat rare diseases and conditions, including in pediatric patients. The US BPCA has been shown as the predominant policy contributing to pediatric drug development for cancer drugs in the US (25). This development is important as many of the drugs exempted by the US PREA have been shown to have a mechanism of action warranting pediatric development plans (26). Second, a spillover effect from the regulatory region with the strongest mandate could occur, however, previous studies have shown only a small number of medicines for pediatric populations arising based on regulatory actions in other regions (27, 28). Lastly, the progress of the pediatric development plans in the EU has been questioned in general and the impact of differences in regulatory requirements could also be reduced if the agreed pediatric development plans are never completed.

Recent numbers suggest that we will continue to see that orphan drug designation compromises around half of the drugs approved in the US (29). However, in the future the difference in mandated pediatric development plans could be reduced as an amendment to the US PREA became effective in August 2020, allowing regulators to mandate a PSP for adult cancer drugs if directed at a molecular target also relevant to the growth or progression of pediatric cancer (30). This amendment also includes required studies for cancer indications with an orphan drug designation.

Our study is the first to suggest a method to investigate the outcome of the broad mandate by the EMA PDCO to require a pediatric drug development that does not only follow the proposed indication by the MA applicant. This is done by tracing the indications only targeted in a PIP in the EU, thereby possibly agreeing to an indication different from the proposed indication, but still within the condition hereof. Using this method, we demonstrate that the EMA PDCO uses this broad mandate to a certain extent and that it contributes to the difference in pediatric requirements mandated by the EMA and the FDA for indications granted at MA. However, the voluntary conduct of requested pediatric studies through the US BPCA is intended for

development outside the proposed indication and could reduce the differences in practice. Unfortunately, such information is not released until the development has been completed and is therefore not publicly available at the time our study was conducted, why we cannot conclude on its contribution. A recent publication showed that after ∼5 years, the potential pediatric use outside an adult indication was rarely included in either the EU or US prescription information (29). This can either be seen as a failure to complete the agreed pediatric development or as a symptom of the complex and long duration of pediatric drug development always being a step behind adult development (31).

Our study also shows an alignment in the EMA and the FDA decisions on pediatric requirements for the indications subject to the mandatory pediatric legislations in both regions. This suggests, that even though a broader basis exists for granting waivers in the US than in the EU, it does not result in any significant differences when pediatric development is required in the two regions. Our findings support previously published findings of Egger et al. (13) who found a high concordance in waiver decisions between the EMA PDCO and FDA. Both agencies are involved in ongoing efforts to harmonize regulatory decisions regarding requirements for pediatric development plans such as the pediatric cluster meetings and guidelines on transparency regarding the advice and agreements of pediatric studies with other regulatory authorities (32, 33). While we cannot claim that the high concordance in decision-making on pediatric development plans observed in this study is a result of these harmonization efforts, their continued use is encouraged.

The results should be interpreted within the limitations of this study. First, the study is a snapshot in time, showing the EMA and the FDA decisions on waivers and pediatric development plans at MA. However, the agreed pediatric development plans are dynamic, with possible modifications after the initial agreement and MA. Second, we did not investigate if the applications for waivers or agreed pediatric development plans were similar in the EU or the US. Instead, we assumed that the basis for the EMA and the FDA decision was similar if similar indications were approved at MA. On the same basis, our study might overestimate the indications only targeted in a PIP, as these could have been derived from earlier proposed indications at the time of application. Third, this study only investigates the mandatory requirements for pediatric development plans without including the voluntary Written Requests issued as part of the US BPCA and does not provide an overview of the entire pediatric development plans taken on by companies in response to pediatric legislations in the US. The potential differences seen from the mandatory legislations could be diminished by a request for pediatric studies through a Written Request (WR) using the US BPCA.

In the subset of indications, where the EU and the US regulators evaluated pediatric requirements on the same grounds, the similarity of the pediatric programs required in both regions remains to be explored. The type of information required in the submission of pediatric development plans is similar (34), but the actual plans with regard to e.g., the number, purpose, design, duration, and timing of required pediatric studies can still differ between regions.

In conclusion, when comparing purely compulsory requirements for pediatric studies for drugs approved in both the EU and the US, a larger number of pediatric development plans were agreed upon in the EU, in line with the broader mandates of the EU Pediatric Regulation. When both regulatory authorities evaluated an indication for requirements for pediatric development plans, they most often made similar decisions regarding waivers and pediatric development plans, and deferrals hereof.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

HC, MD, and CH wrote the manuscript and designed the research. HC and CH performed the research. HC analyzed the data. All authors contributed to the article and approved the submitted version.

Funding

HC is a Ph.D. student at CORS and project was funded by a grant from Lundbeck A/S to the Copenhagen Centre for Regulatory Science (CORS) at the University of Copenhagen. CORS is a cross-faculty university-anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals, LEO pharma) as well as patient organizations (Rare Diseases Denmark). The center is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus. The research is not a company-specific product or directly company-related.

Acknowledgments

We thank the Centre for Innovation in Regulatory Science (CIRS) for providing us with a digital list of all new active substances approved by EMA and the FDA. We also thank Stine Moesbo Larsen for her valuable help with data collection. MedDRA® trademark is registered by IFPMA on behalf of ICH.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1009432/full#supplementary-material

References

1. WHO report. *Paediatric Regulators Network Meeting: Report to WHO concerning international guidelines for paediatric medicines*. (2010). Available online at: https://www.who.int/childmedicines/paediatric_regulators/International_guidelines.pdf (accessed February 2022).

2. European Commission. *Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004*. (2006). Available online at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1901&from=EN (accessed February 2022).

3. FDA. *Pediatric Research Equity Act of 2003*. (2003). Available online at: https://www.congress.gov/108/plaws/publ155/PLAW-108publ155.pdf (accessed February 2022).

4. FDA. *Best Pharmaceuticals for Children Act of 2002*. (2002). Available online at: https://www.congress.gov/107/plaws/publ109/PLAW-107publ109.pdf (accessed February 2022).

5. Penkov D, Tomasi P, Eichler I, Murphy D, Yao LP, Temeck J. Pediatric medicine development: an overview and comparison of regulatory processes in the European Union and United States. *Ther Innov Regul Sci.* (2017) 51:360–71. doi: 10.1177/2168479017696265

6. Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: the impact of evolving regulations. *Adv Drug Deliv Rev.* (2014) 73:2–13. doi: 10.1016/j.addr.2014.02.003

7. EMA. *Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver)*. (2012). Available online at: https://www.ema.europa.eu/en/documents/other/policy-determination-conditions-paediatric-investigation-plan-pip/waiver-scope-pip/waiver_en.pdf (accessed June 2022).

8. EMA and FDA. *Principles of Interactions: Between EMEA and FDA Pediatric Therapeutics*. (2007). Available online at: https://www.ema.europa.eu/en/documents/other/principles-interactions-between-european-medicines-agency-food-drug-administration-paediatric_en.pdf (accessed June 2022).

9. Sable CA, Ivy DD, Beekman RH, Jeter H, Jankins K, Mahle W, et al. 2017 ACC/AAP/AHA health policy statement on opportunities and challenges in pediatric drug development: learning from sildenafil. *Circ Cardiovasc Qual Outcomes*. (2017) 70:495–503. doi: 10.1161/HCQ.0000000000000026

10. Chin WW, Joos A. Moving toward a paradigm shift in the regulatory requirements for pediatric medicines. *Eur J Pediatr.* (2016) 175:1881–91. doi: 10.1007/s00431-016-2781-z

11. EMA. *10-year Report to the European Commission - General report on the experience acquired as a result of the application of the Paediatric Regulation.* (2017). Available online at: https://ec.europa.eu/health/system/files/2020-06/paediatrics_10_years_ema_technical_report_0.pdf (accessed June 2022).

12. Davies E.H, Ollivier CM, Saint Raymond A. Paediatric investigation plans for pain: painfully slow! *Eur J Clin Pharmacol.* (2010) 66:1091–7. doi: 10.1007/s00228-010-0886-2

13. Egger GF, Wharton GT, Malli S, Temeck J, Murphy MD, Tomasi P, et al. Comparative review of waivers granted in pediatric drug development by FDA and EMA from 2007-2013. *Ther Innov Regul Sci.* (2016) 50:639–47. doi: 10.1177/2168479016646809

14. Centre for Innovation in Regulatory Science. *R&D Briefing 67: New drug approvals in six major authorities 2008 – 2017: Focus on the availability of medicines company size*. CIRS. London UK. (2018). Available online at: https://cirsci.org/wp-content/uploads/dlm_uploads/2021/01/RD-67-04052018_FINAL-6-agency.pdf (accessed October 20, 2022).

15. Centre for Innovation in Regulatory Science. *R&D Briefing 77: New drug approvals in six major authorities 2010 – 2019: Focus on Facilitated Regulatory Pathways and Internationalisation.* (2010). Available online at: https://cirsci.org/wp-content/uploads/2020/06/CIRS-RD-Briefing-77-6-agencies.pdf (accessed October 20, 2022).

16. FDA. *Drugs@FDA: FDA-Approved Drugs: FDA. Approval information of products approved by Center for Drug Evaluation and Research (CDER).* Available online at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

17. FDA. *Licensed Biological Products with Supporting Documents. Approval information of products approved by Center for Biologics Evaluation and Research (CBER).* Available online at: https://www.fda.gov/vaccines-blood-biologics/licensed-biological-products-supporting-documents.

18. EMA. *Download medicine data.* Available online at: https://www.ema.europa.eu/en/medicines/download-medicine-data#european-public-assessment-reports-(epar)-section.

19. EMA. *Access-to-documents request.* Available online at: https://ec.europa.eu/transparency/regdoc/index.cfm?fuseactioN=~fmb&language=en.

20. Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1 September 2019. (2019). Available online at: https://www.meddra.org/howto-use/support-documentation/english (accessed October 20, 2022).

21. European Medicines Agency. *ICH. Topic E 11: Clinical Investigation of Medicinal Products in the Paediatric Population*. London: European Medicines Agency (2001).

22. R Core Team (2021). *R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria*. Available online at: https://www.R-project.org/ (accessed October 20, 2022)..

23. Giannuzzi V, Conte R, Landi A, Ottomano SA, Bonifazi D, Balardi P, et al. Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen. *Orphanet J Rare Dis.* (2017) 12:64. doi: 10.1186/s13023-017-0617-1

24. Christiansen H, Bruin ML, Frokjaer S, Hallgreen CE. Guidance for pediatric use in prescription information for novel medicinal products in the EU and the US. *PLoS ONE.* (2022) 17: e0266353. doi: 10.1371/journal.pone.0266353

25. Akalu AY, Meng X, Reaman GH, Ma L, Yuan W, Ye J, et al. Review of the experience with pediatric written requests issued for oncology drug products. *Pediatr Blood Cancer.* (2021) 68: e28828. doi: 10.1002/pbc.28828

26. Pearson ADJP, et al. *From class waivers to precision medicine in paediatric oncology Lancet Oncol.* (2017) 18:e394–404. doi: 10.1016/S1470-2045(17)30442-4

27. Oortwijn WJ, Horlings E, Anton S, Loo M, Kahan JP. *Extended Impact Assesment of a Draft EC regulation on Medicinal Products for Paediatric Use. RAND Europe.* (2004). Available online at: https://www.rand.org/content/dam/rand/pubs/monographs/2004/RAND_MG308.pdf (accessed October 20, 2022)..

28. Chui J, Tordoff J, Reith D. Changes in availability of paediatric medicines in Australia between 1998 and 2002. *Br J Clin Pharmacol.* (2005) 59:736–42. doi: 10.1111/j.1365-2125.2004.02211.x

29. Kinch MS, Kraft Z, Schwartz T. 2020 in review: FDA approvals of new medicines. *Drug Discov*. (2021) 26:2794–9. doi: 10.1016/j.drudis.2021.07.003

30. FDA. *Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act. Guidance for Industry*. (2019). Available online at: https://www.fda.gov/media/133440/download (accessed October 20, 2022)..

31. Neel DV, Shulman DS, DuBois SG. Timing of first-in-child trials of FDA-approved oncology drugs. *Eur J Cancer*. (2019) 112:49–56. doi: 10.1016/j.ejca.2019.02.011

32. FDA. *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry*. (2020). Available online at: https://www.fda.gov/media/86340/download (accessed October 20, 2022)..

33. EMA. *Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies*. (2014). Available online at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52014XC0927(01)&from=EN (accessed October 20, 2022).

34. Thomsen MDT. Global pediatric drug development. *Curr Ther Res Clin Exp.* (2019) 90:135–42. doi: 10.1016/j.curtheres.2019.02.001

Frontiers in Medicine

Translating medical research and innovation into improved patient care

A multidisciplinary journal which advances our medical knowledge. It supports the translation of scientific advances into new therapies and diagnostic tools that will improve patient care.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact