**Supplementary Table 1:** Adapted version of Critical Appraisal Skills Programme (CASP)21 cohort study checklist, which was also applied to placebo arms of clinical trials.

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| **Adapted CASP tool**  |
| 1. Clearly focused study population? | a. Adults with PD |
| 2. No selection bias? | a. Represents the population of interestb. Origin of study group stated clearlyc. Information on PD duration available |
| 3. Ascertainment of diagnosis? | a. Validated diagnostic criteria for Parkinson's disease specified |
| 4. Adequate measurement of outcomes? | a. Objective outcome measure defined and referencedb. Relationship of motor assessment to medication cycle statedc. Low risk of attrition bias: dropout rate not excessive, reasons for dropout providedd. Observation period >3 yearse. Three or more time points, including baselinef. Patient number >50 |
| 5. Results | a. Mean and standard deviation (or values from which these can be calculated) available on each timepoint in published material |
| DETERMINATION OF RISK OF BIAS | Based on criteria listed above, each question was allocated a grading for risk of bias: low (green), moderate (orange) and high (red).The overall risk of bias for an article was determined according to the following formulae:Low risk of bias: * 1 yellow, 4 green
* 2 yellow, 3 green
* 1 red, 1 yellow, 3 green

Moderate risk of bias:* 3 yellow, 2 green
* 4 yellow, 1 green
* 1 red, 2 yellow, 2 green
* 2 red 2 yellow, 1 green

High risk of bias:* 3 or more red

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**Supplementary Table 2.** Study characteristics. R = calculable rate of motor progression, M = meta-analysis, S = data simulation, C = simultaneous commencement of levodopa, P = prodromal; PD = Parkinson’s disease; p.a. = per annum; n/a = not available.

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| **Author, year** | **Analysis** | **Study type** | **Baseline sample size** | **Baseline age (years)** | **Baseline PD duration(years)** | **Study duration(years)** | **Motor scale (maximum score)** | **Motor assessment in relation to medication cycle** | **Motor progression rate** |
| Alarcon, 1998 24 | R, C | Clinical trial | 38 | 64 | 4.1 | 3.0 | UPDRS-III (108) | Prevailing | 0.4% p.a. |
| Allain, 2000 25 | R, M, S | Clinical trial | 41 | 60 | 1.7 | 5.0 | UPDRS-III (108) | Prevailing | 1.0% p.a. |
| Alves, 2005 26 | R, M, S | Population | 232 | 74 | 9.1 | 8.0 | UPDRS-III (108) | Prevailing | 2.2% p.a. |
| Antonini, 2012 27 | R, M, S | Cohort | 707 | 67 | n/a | 2.0 | UPDRS-III (108) | Prevailing | 1.6% p.a. |
| Athauda, 2017 28 | R, M, S | Clinical trial | 29 | 58 | 6.4 | 1.2 | MDS-UPDRS-III (132) | Off | 1.3% p.a. |
| On | 0.2% p.a. |
| Athauda, 2022 29 | R, M, S | Cohort | 1930 | 68 | 1.3 | 3.0 | MDS-UPDRS-III (132) | Prevailing | 1.7% p.a. |
| Aviles-Olmos, 2013 101  | R, M, S | Clinical trial | 24 | 59 | 11 | 1 | MDS-UPDRS-III (132) | Off | 1.7% p.a. |
| On | 2.7% p.a. |
| Ayala, 2017 30 | R, M, S | Cohort | 205 | 66 | 8.1 | 3.0 | SCOPA mot 42 (30) | Prevailing | 1.6% p.a. |
| Carvalho, 2023 31 | R, M, S | Cohort | 98 | 68 | 4.6 | 2.0 | MDS-UPDRS-III (132) | On | 0.9% p.a. |
| Chan, 2023 105 | R, M, S | Cohort | 103 | 68 | 2.7 | 1 | UPDRS-III (108) | Prevailing | -1.2% p.a. |
| Cilia, 2020 32 | R, M, S, C | Cohort | 30 | 64 | 7.1 | 2.0 | UPDRS-III (108) | Off | 3.4% p.a. |
| On | 1.3% p.a. |
| Davidson, 2012 33 | C | Population | 133 | 71 | n/a | 1.0 | UPDRS-III (108) | n/a | n/a |

**Supplementary Table 2** (continued).

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **Analysis** | **Study type** | **Baseline sample size** | **Baseline age (years)** | **Baseline PD duration(years)** | **Study duration(years)** | **Motor scale (maximum score)** | **Motor assessment in relation to medication cycle** | **Motor progression rate** |
| Davis, 2016 102 | R, M | Cohort | 733 | 68 | 8.7 | 3.0 | MDS-UPDRS-III (132) | Prevailing | 1.6% p.a. |
| Deng, 2019 34 | R, M, S | Cohort | 156 | 65 | 0.2 | 9.0 | UPDRS-III (108) | On | 1.0% p.a. |
| Devos, 2022 108 | R, M, S | Clinical trial | 186 | 63 | 1.1 | 0.7 | MDS-UPDRS-III (132) | Untreated | 4.4% p.a. |
| Ding, 2016 35 | R, M, S, C | Cohort | 34 | 64 | 1.7 | 20.3 | Mod Webster (36) | Off | 2.0% p.a. |
| On | 1.3% p.a. |
| Duarte Folle, 2019 41 | R, M, S | Cohort | 776 | 71 | 3.0 | 3.4 | UPDRS-III (108) | Off | 0.0% p.a. |
| Dupont, 1996 36 | R, M, S | Clinical trial | 69 | 66 | 2.7 | 5.0 | Webster (30) | On | 5.0% p.a. |
| Eggers, 2012 37 | R, M, S | Cohort | 27 | 59 | 3.8 | 2.5 | UPDRS-III (108) | Off  | 1.8% p.a. |
| On | 1.2% p.a. |
| Evans, 2011 38 | R | Population | 122 | n/a | 0.4 | 7.9 | UPDRS-III (108) | On | 2.1% p.a. |
| Fahn (PSG), 2004 39 | R, M | Clinical trial | 90 | 65 | 0.4 | 0.8 | UPDRS-III (108) | Untreated | 6.9% p.a. |
| Fereshtehnejad, 2019 40 | P | Cohort | 154 | n/a | n/a | n/a | UPDRS-III (108) | n/a | n/a |
| Frazzitta, 2012 42 | R, M, S | Clinical trial | 25 | 70 | 9.0 | 1.0 | UPDRS-III (108) | On | 5.6% p.a. |
| Fu, 2022 43 | R, M, S | Cohort | 234 | 66 | 5.0 | 5.0 | UPDRS-III (108) | On | 0.4% p.a. |
| Gago, 2009 44 | R, M | Cohort | 24 | 64 | 5.0 | 6.0 | UPDRS-III (108) | Prevailing | 3.8% p.a. |
| García, 2022 88 | R, M | Cohort | 511 | 63 | 5.3 | 2.0 | UPDRS-III (108) | Off | 1.5% p.a. |
| García-Ruiz, 2004 45 | R, M, S | Cohort | 59 | 62 | n/a | 5.0 | UPDRS-III (108) | Prevailing | 1.3% p.a. |

**Supplementary Table 2** (continued). \*Patients were assessed in both *off* and *on* state, but this was not defined *off* and *on* after testdose.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **Analysis** | **Study type** | **Baseline sample size** | **Baseline age (years)** | **Baseline PD duration(years)** | **Study duration(years)** | **Motor scale (maximum score)** | **Motor assessment in relation to medication cycle** | **Motor progression rate** |
| Helmy, 2022 46 | R, M, S | Cohort | 45 | 57 | 4.9 | 1.0 | MDS-UPDRS-III (132) | Off | 8.8% p.a. |
| Hely, 1994 47 | R, C | Clinical trial | 64 | 62 | 2.1 | 5.0 | Mod Columbia (102) | Prevailing | 1.6% p.a. |
| Holden, 2018 48 | R, M, S | Cohort | 362 | 61 | n/a | 5.0 | MDS-UPDRS-III (132) | Off | 1.8% p.a. |
| Holloway, 2004 49 | R, M, S, C | Clinical trial | 150 | 61 | 1.8 | 4.0 | UPDRS-III (108) | Prevailing | 1.7% p.a. |
| Hughes, 1994 50 | R | Cohort | 23 | 57 | 12.0 | 3.1 | Mod Webster (36) | Off | 4.5% p.a. |
| On | 4.3% p.a. |
| Imarisio, 2022 51 | R, M, S | Cohort | 71 | 65 | 5.2 | 2.0 | MDS-UPDRS-III (132) | Prevailing | 0.6% p.a. |
| Jankovic, 2001 52 | R | Cohort | 297 | 61.6 | 6.5 | 6.4 | UPDRS-III (108) | Off \*On \* | 1.3% p.a.0.7% p.a. |
| Joza, 2023 53 | P | Cohort | 1160 | n/a | n/a | 3.3 | MDS-UPDRS-III (132) | n/a | n/a |
| Katzenschlager, 2008 54 | R, M, S, C | Clinical trial | 249 | 57 | 1.6 | 12.0 | Mod Webster (36) | Prevailing | 2.4% p.a. |
| Kraus, 2005 55 | R, M, S | Cohort | 411 | 62 | n/a | 4.0 | Webster (30) | Prevailing | 2.0% p.a. |
| Lang, 2022 109 | R, M, S | Clinical trial | 100 | 61 | 0.7 | 1.0 | MDS-UPDRS-III (132) | Untreated | 4.6% p.a. |
| Larsen, 1999 56 | R, M, S, C | Clinical trial | 81 | 64 | 2.0 | 5.0 | UPDRS-III (108) | On | 2.0% p.a. |
| Lenfeldt, 2013 57 | R, M, S | Cohort | 66 | 69 | n/a | 5.0 | UPDRS-III (108) | Prevailing | 0.8% p.a. |
| Lewis, 2020 58 | R, M | Cohort | 80 | 68 | 3.8 | 3.0 | MDS-UPDRS-III (132) | On | 0.0% p.a. |
| Li, 2018 59 | R, M, S | Cohort | 23 | 55 | 5.6 | 1.6 | UPDRS-III (108) | Off | 2.4% p.a. |
| Lopez, 2010 60 | R, M, S | Cohort | 64 | n/a | n/a | 10.0 | UPDRS-III (108) | Prevailing | 1.5% p.a. |
| Louis, 1999 61 | R | Cohort | 237 | 73 | 6.8 | 7.0 | modUPDRS-III (100) | Prevailing | 1.5% p.a. |

**Supplementary Table 2** (continued).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **Analysis** | **Study type** | **Baseline sample size** | **Baseline age (years)** | **Baseline PD duration(years)** | **Study duration(years)** | **Motor scale (maximum score)** | **Motor assessment in relation to medication cycle** | **Motor progression rate** |
| Lubomski, 2022 62 | R, M, S | Cohort | 82 | 67 | 8.6 | 1.0 | MDS-UPDRS-III (132) | On | 4.5% p.a. |
| Ludin, 1976 63 | R, M, S, C | Cohort | 35 | 56 | n/a | 3.0 | Webster (30) | Prevailing | 4.5% p.a. |
| Maple-Grødem, 2021 104 | R, M | Population | 440 | 70 | 2.1 | 7 | UPDRS-III (108) | Prevailing | 1.3% p.a. |
| Melzer, 2015 110 | R, M | Cohort | 23 | 70 | 5.6 | 1 | MDS-UPDRS-III (132) | Prevailing | -1.4% p.a. |
| Merola, 2016 64 | R, M, S | Cohort | 20 | 62 | 14.1 | 5.1 | UPDRS-III (108) | Off | 2.5% p.a. |
| On | 0.9% p.a. |
| Miller-Patterson, 2020 65 | P | Population | 205 | 83 | n/a | 3.8 | UPDRS-III (108) | n/a | n/a |
| Moccia, 2016 66 | R, M, S | Cohort | 79 | 64 | 1.2 | 4 | UPDRS-III (108) | Off | 1.7% p.a. |
| Mollenhauer, 2019 67 | R, M, S | Cohort | 135 | 65 | n/a | 4.0 | MDS-UPDRS-III (132) | Prevailing | 1.4% p.a. |
| Muslimović, 2009 14 | R, M, S | Cohort (new onset) | 116 | 65 | 1.5 | 3.0 | UPDRS-III (108) | On | 2.5% p.a. |
| Cohort (established) | 64 | 65 | 6.4 | 3.0 | UPDRS-III (108) | On | 0.6% p.a. |
| Myllylä, 1992 68 | R, M, S | Clinical trial | 25 | 61 | 1.8 | 1.0 | CURS (100) | Untreated | 6.7% p.a. |
| Myllylä, 1995 69 | R, M, S, C | Clinical trial | 21 | 60 | 1.7 | 2.0 | CURS (100) | Prevailing | 3.2% p.a. |
| Ng, 2015 70 | R, M, S | Cohort | 81 | 65 | 5.4 | 1.5 | UPDRS-III (108) | Prevailing | 0.9% p.a. |
| O'Suilleabhain, 2006 71 | R, M, S | Cohort | 79 | 65 | 3.7 | 2.0 | UPDRS-III (108) | Prevailing | 0.3% p.a. |
| Oertel, 2006 72 | R, M, S, C | Clinical trial | 146 | 59 | n/a | 3.0 | UPDRS-III (108) | Prevailing | 1.3% p.a. |
| Olanow, 1995 73 | R, M, S, C | Clinical trial | 21 | 66 | 3.0 | 1.0 | UPDRS-III (108) | Prevailing | 0.5% p.a. |

**Supplementary Table 2** (continued).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **Analysis** | **Study type** | **Baseline sample size** | **Baseline age (years)** | **Baseline PD duration(years)** | **Study duration(years)** | **Motor scale (maximum score)** | **Motor assessment in relation to medication cycle** | **Motor progression rate** |
| Olanow, 2006 74 | R | Clinical trial | 71 | 61 | 0.9 | 1.0 | UPDRS-III (108) | Prevailing | 4.8% p.a. |
| Ou, 2021 75 | R, M, S | Cohort | 224 | 58 | 1.5 | 3.0 | UPDRS-III (108) | Prevailing | 1.8% p.a. |
| Pagano, 2022 107 | R, M, S | Clinical trial | 105 | 60 | 0.8 | 1 | MDS-UPDRS-III (132) | Untreated | 4.2% p.a. |
| Palermo, 2021 76 | R, M, S | Cohort | 104 | n/a | n/a | 4.0 | MDS-UPDRS-III (132) | Off | 1.2% p.a. |
| Pålhagen, 1998 78 | R, M | Clinical trial | 76 | 64 | 1.9 | 1.0 | UPDRS-III (108) | Untreated | 2.4% p.a. |
| Pålhagen, 2007 77 | R, M, S, C | Clinical trial | 68 | 64 | 1.9 | 6.5 | UPDRS-III (108) | On | 2.4% p.a. |
| Pilotto, 2021 100 | R, M, S | Cohort | 92 | 66 | 5.5 | 2.0 | MDS-UPDRS-III (132) | Prevailing | 0.9% p.a. |
| Pirker, 2003 79 | R, M, S | Cohort | 21 | 56 | 2.4 | 5.3 | UPDRS-III (108) | Off | 2.8% p.a. |
| On | 2.4% p.a. |
| Rascol, 2000 81 | R, M, S, C | Clinical trial | 89 | 63 | 2.4 | 5.0 | UPDRS-III (108) | Prevailing | 0.8% p.a. |
| Rascol, 2011 5 | R | Clinical trial | 588 | n/a | n/a | 0.7 | UPDRS-III (108) | Untreated | 1.9% p.a. |
| Ravina, 2012 82 | R, M, S | Cohort | 491 | 60 | 0.8 | 5.5 | UPDRS-III (108) | Prevailing | 0.8% p.a. |
| Reinoso, 2014 83 | R, M, S | Cohort | 576 | 64 | n/a | 9.0 | UPDRS-III (108) | On | 1.2% p.a. |
| Rinne, 1997 84 | C | Clinical trial | 205 | 63 | 2.0 | 1.0 | UPDRS-III (108) | n/a | n/a |
| Rinne, 1998 85 | R, C | Clinical trial | 204 | 61 | 1.9 | 4.0 | UPDRS-III (108) | Prevailing | 2.0% p.a. |
| Ritz, 2012 106 | R, M | Population | 222 | 69 | 1.9 | 5.1 | UPDRS-III (108) | Off | 2.4% p.a. |
| Ryu, 2022 86 | R, M, S | Cohort | 120 | 65 | 0.7 | 3.1 | UPDRS-III (108) | Prevailing | 1.2% p.a. |

**Supplementary Table 2** (continued).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **Analysis** | **Study type** | **Baseline sample size** | **Baseline age (years)** | **Baseline PD duration(years)** | **Study duration(years)** | **Motor scale (maximum score)** | **Motor assessment in relation to medication cycle** | **Motor progression rate** |
| Santaella, 2020 87 | R, M | Cohort | 46 | 58 | 3.0 | 3.0 | UPDRS-III (108) | Off | 0.5% p.a. |
| Schenkman, 2018 89 | R, M, S | Clinical trial | 40 | 64 | 0.4 | 0.5 | MDS-UPDRS-III (132) | Prevailing | 4.8% p.a. |
| Schrag, 2007 90 | R, M, S | Cohort | 145 | 67 | 9.3 | 1.0 | UPDRS-III (108) | Prevailing | 2.7% p.a. |
| Schreiner, 2019 91 | R, M, S | Cohort | 129 | 63 | 5.4 | 4.6 | UPDRS-III (108) | Prevailing | 1.0% p.a. |
| Shoulson, 2007 103 | R, M | Clinical trial | 191 | 60 | 0.9 | 1.8 | UPDRS-III (108) | Prevailing | 2.9% p.a. |
| Shoulson (PSG), 1989 4 | R, M,  | Clinical trial | 401 | 61 | 2.2 | 1.0 | UPDRS-III (108) | Untreated | 7.9% p.a. |
| Siderowf, 2020 92 | P | Cohort | 303 | n/a | n/a | 6.3 | UPDRS-III (108) | n/a | n/a |
| Simuni (NINDS), 2015 93 | R, M | Clinical trial | 71 | 59 | 2.3 | 0.8 | UPDRS-III (108) | Prevailing | 4.2% p.a. |
| Simuni (PSG), 2020 80 | R, M, S | Clinical trial | 166 | 62 | 0.9 | 3.0 | UPDRS-III (108) | Off | 1.4% p.a. |
| Sleeman, 2017 94 | R, M, S | Cohort | 145 | 66 | 0.5 | 3.0 | MDS-UPDRS-III (132) | Prevailing | 2.9% p.a. |
| Suzuki, 2013 95 | R, M | Clinical trial | 58 | 71 | 1.1 | 1.0 | UPDRS-III (108) | Prevailing | 1.0% p.a. |
| Velseboer, 2013 96 | R, M, S | Cohort | 129 | 67 | 1.7 | 5.0 | UPDRS-III (108) | Prevailing | 2.0% p.a. |
| Vogt, 2011 97 | R, M, S | Cohort | 44 | 59 | 2.0 | 3.7 | UPDRS-III (108) | Off | 2.6% p.a. |
| Yu, 2020 98 | R, M, S | Cohort | 246 | 57 | 4.8 | 2.0 | MDS-UPDRS-III (132) | Prevailing | 1.7% p.a. |
| Zangaglia, 2009 99 | R, M, S | Clinical trial | 33 | 63 | 10.0 | 3.0 | UPDRS-III (108) | Off | 1.7% p.a. |
| On | 1.4% p.a. |