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‘Being disabled’ as an exclusion criterion for clinical trials: a scoping review

Guido Camanni ,[1] Ornella Ciccone,[1] Alessandro Lepri,[1] Chiara Tinarelli,[1] Chiara Bedetti,[2] Sandra Cicuttin,[1] Nicola Murgia,[3] Sandro Elisei[1]

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[1]Rehabilitation Unit, Istituto Serafico, Assisi; Perugia, Italy
[2]Department of Neurology, Città di Castello Hospital, Citta di Castello, Italy
[3]Department of Environmental Science and Prevention, University of Ferrara, Ferrara, Italy

Correspondence to
Dr Guido Camanni;
guidocamanni@serafico.it

ABSTRACT

Background People with disabilities (PWDs) are often excluded from biomedical research, but comprehensive data regarding their participation in clinical trials are not available. The objective of this study was to assess the rates of exclusion of PWDs from recent medical scientific research.

Methods The protocol of the study was designed according to PRISMA-ScR (PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for Scoping Reviews) guidelines. All completed interventional clinical trials registered on ClinicalTrials.gov between 2010 and 2020 regarding the 10 leading causes of global disability-adjusted life-years according to the Global Burden of Disease Study were analysed. An exclusion criterion from the study was considered explicit if it could be associated with one of the following seven categories: disability, physical impairment, cognitive impairment, behavioural or psychiatric disorders, language and communication impairment, sensory impairment. Comorbidities not more clearly defined and researcher discretion regarding exclusion of study participants were considered to be ‘implicit exclusion criteria’. We assessed the appropriateness of explicit exclusion criteria in relation to the primary objectives of the trials and labelled them as ‘absolute’, ‘relative’ or ‘questionable’.

Results The total number of trials analysed was 2710; 170 were paediatric trials (6.3%), 2374 were adult trials (87.6%) and 166 were trials including subjects of all ages (6.1%). Explicit exclusion criteria were found in 958 trials (35.3%). The disability category most frequently excluded was behavioural or psychiatric disorders, present in 588 trials (61.4%). In only 3% and 1% of the trials, the exclusion criteria were considered either ‘absolute’ or ‘questionable’, while in 96% the exclusion criteria were judged as ‘relative’. Implicit exclusion criteria were present in 1205 trials (44.5%).

Conclusions This study highlights the high rate of exclusion of PWDs from biomedical research and the widespread use of ill-defined exclusion criteria in clinical trials. It underscores the importance of more inclusive study designs so that PWDs can become active participants in research.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The systematic absence of a minority from biomedical research makes it unclear whether the scientific knowledge obtained so far can be applied to that minority as well.
⇒ There is a growing sensitivity towards the issue of exclusion of people with disabilities from biomedical research.

WHAT THIS STUDY ADDS

⇒ The significant number of trials analysed allows for a more accurate quantification of the extent of the problem of exclusion of people with disabilities from research.
⇒ This study analyses the different disability categories and facilitates the assessment of which category is at greater risk of exclusion.
⇒ The study also analyses the appropriateness of the exclusion of people with disabilities in relation to the primary objectives of clinical trials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the importance of more inclusive study designs so that people with disabilities can become active participants in biomedical research.

INTRODUCTION

An estimated of 1.3 billion people, 16% of the global population worldwide, experience a significant disability today.[1] The WHO reports that the number of people with disabilities (PWDs) has increased during the past decade due to different demographic and epidemiological changes such as world population growth, the increased number of people with non-communicable diseases, longer life expectancy and ageing with associated limitations in functioning. PWDs access health services more frequently than people without disabilities.[2] Despite the high number of PWDs in the world and the highest rate of access to care, PWDs are largely underrepresented in large-scale biomedical research.[3 4] Feldman *et*

al examined the exclusion rate for children with disabilities from mainstream developmental research published in high-impact journals. The authors found that 66.7% of articles mentioning disability explicitly excluded those children.[5] Schwartz and Unni, in their systematic review of 182 studies included in the Cochrane Review on Interventions for Enhancing Medication Adherence, found a 32% exclusion rate for persons with cognitive impairment, 7% for persons with visual impairment, 3% for persons with motor impairment and 1% for persons with hearing impairment.[6] DeCormier Plosky *et al*, in their review of 97 clinical research protocols selected from the database ClinicalTrials.gov, found the following rates of exclusion in disability-related domains: 68% rate of exclusion for the psychiatric, 42% for cognitive or intellectual, 34% for visual, 10% for hearing, 9% for mobility and 3% for communication domains. Furthermore, they found that in 85% of the trials the investigators were allowed to exclude participants at their discretion.[7]

Clinical trials are the most reliable interventional studies for providing meaningful scientific evidence regarding the efficacy of new drugs or interventions.[8] The risk of selection bias and the risk of confounding factors influencing the results are minimised in clinical trials by randomisation and blinding.[9] External validity, defined as the applicability of the results to a real-world population larger than the study group, significantly influences the actual usefulness of a study. Assessing the external validity of a clinical trial requires careful analysis of the eligibility criteria and the setting in which the trial was carried out: temporal aspects, ethnical, geographical and socioeconomic differences between study population and target population are all factors, which may affect the results obtained in the trial and thus their interpretation in other contexts.[10] In a clinical trial, the set of inclusion and exclusion criteria constitute the eligibility criteria: a set of requirements that a participant must, respectively, possess or not possess in order to be included in the trial. Van Spall *et al*[11] examined the incidence of poorly justified exclusion and inclusion criteria in published clinical trials in high-impact journals between 1994 and 2006 by using a series sampling technique; they found that over 80% of the trials comprised at least one hardly justified exclusion criterion.[11] Although providing adequate information regarding eligibility criteria is a key point in assessing the external validity of a study, a concern clearly reiterated in the CONSORT 2010 statement and guidelines[12], it is the lack of attention given to assessing the external validity of a study which explains why many trials either do not report eligibility criteria in detail or often contain vague and ill-defined criteria.[12–14] Both highly selective trial eligibility criteria and excessive discretion of researchers in selecting study participants may lead to poor levels of external validity.[15 16] Persons with disabilities are often excluded from scientific research because they are considered frail and at greater risk of complications due to frequent comorbidities. This might reinforce an unwillingness by researchers to deal with people who are uncooperative or who have communication difficulties.[17 18]

We conducted a scoping review to analyse the exclusion rate of PWDs in a large number of interventional clinical trials on common conditions/diseases affecting the general population and to evaluate the appropriateness of the exclusion criteria presented. Our perspective is that common conditions/diseases in the general population may also affect PWDs, therefore, their exclusion from clinical trials may prejudice their rights to participate in research and produce results that might not be applicable to them. The disease categories we wanted to analyse had to impact global health not only geographically but also in terms of mortality and years of life with disability. The Global Burden of Disease (GBD) is considered a comprehensive assessment of mortality and disability from diseases, injuries and risk factors worldwide. Among the parameters used in GBD we considered disability-adjusted life-years (DALYs), a parameter that encompasses both perspectives we wanted to study: mortality (expressed as Years of life lost (YLLs)) and years living with disability.[19] Our goal is to provide elements to support ongoing thinking within the scientific community advocating for increased inclusivity in biomedical research allowing for PWDs, as well as other members of minority groups, to become more active participants in the research process.

METHODS

Design

The protocol of the study was designed according to PRISMA extension for scoping reviews guidelines. The study consisted of evaluating the exclusion rates of health conditions and impairments associated with disability, in clinical trial protocols selected from the ClinicalTrials.gov database concerning the 10 diseases with the greatest morbidity and mortality levels as indicated in the GBD Study 2017.

Information sources, search and eligibility criteria

A search was conducted of the top 20, level 3, leading causes of global DALYs in male and female lists according to the GBD study, published in The Lancet in September 2018.[19] We selected the first 10 causes present in both lists: diabetes, neonatal disorders, ischaemic heart disease, stroke, lower respiratory infections/pneumonia, diarrhoea, chronic obstructive pulmonary disease (COPD), low back pain, headache disorders and congenital defects. The website ClinicalTrials.gov was consulted for the review starting on 31 December 2021 to search for all completed, interventional clinical trials with results, with start study date between 30 June 2010 and 30 June 2020, using the top 10 causes of DALYs as keywords. Trials appearing in more than one of the 10 leading causes of DALYs were assigned to the group of pathologies most closely related to the primary objective of the

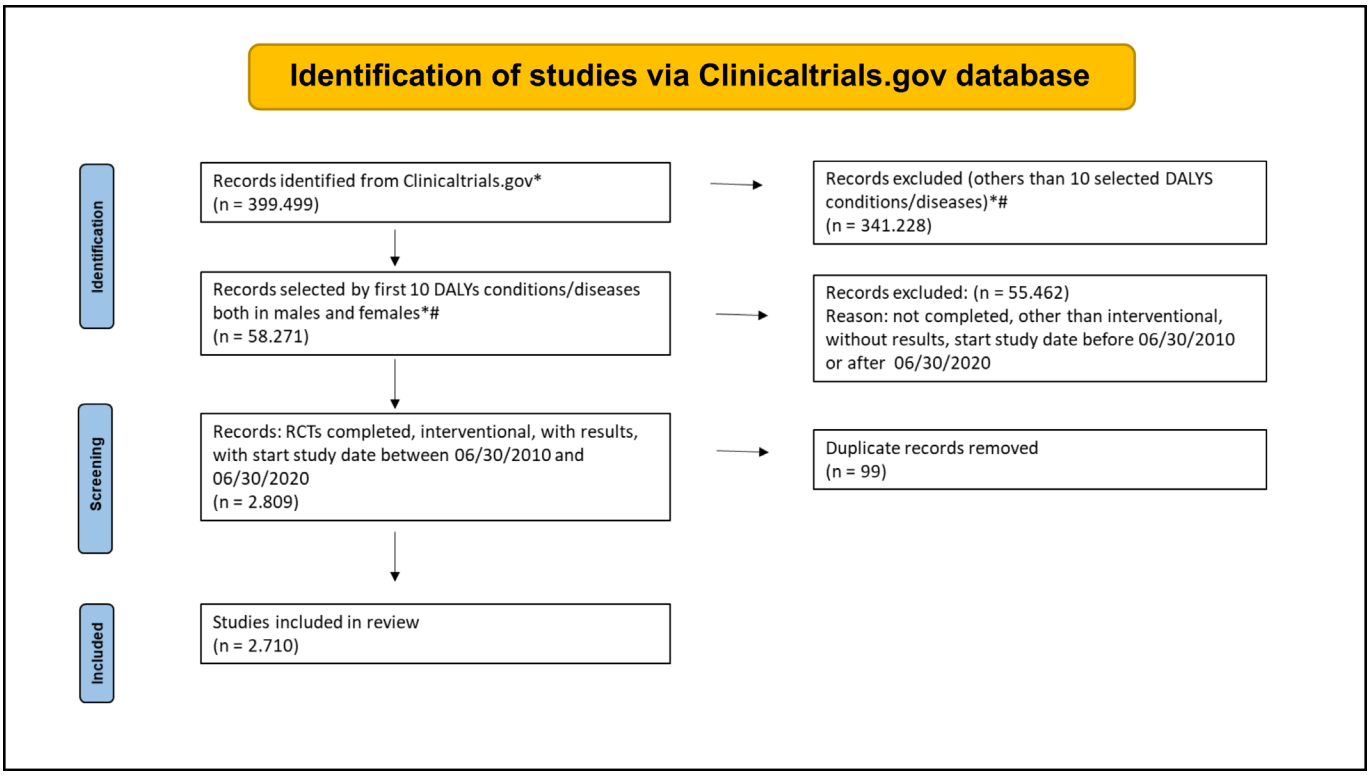

Figure 1 PRISMA flow diagram for the scoping review process. *Number of records by 31 December 2021 (https://classic.clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime). #Global Burden of Disease Study, The Lancet on September 2018. First 10 causes present in both male and female lists: Diabetes, neonatal disorders, ischaemic heart disease, stroke, lower respiratory infections/pneumonia, diarrhoea, COPD, low back pain, headache disorders and congenital defects. COPD, chronic obstructive pulmonary disease; DALY, disability-adjusted life-year; RCT, Randomized controlled trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

trial. Duplicates or triplicates of trials were subsequently excluded (figure 1).

Outcome data extraction and categorisation

Trials were analysed and classified according to the main causes of DALYs and divided among the individual researchers. The features analysed were number and age of study participants, study start date, type of interventional clinical trial (pharmacological, surgical, non-pharmacological, non-surgical and diagnostic trials), presence of masking and inability to give informed consent.

'Explicit' exclusion criteria for PWDs were expressed as disability (not otherwise specified), physical impairment, cognitive impairment, behavioural or psychiatric disorders, communication and language impairment, visual impairment/blindness and hearing impairment/deafness (sensory disabilities). The presence of one or more of the above explicit exclusion criteria for PWDS was searched in both exclusion criteria and inclusion criteria. The researchers evaluated the 'explicit exclusion criteria' present in the trials as:

1. Absolute exclusion criterion: a condition of the PWDs that, in relation to the primary objective of the study, made the evaluation of the researcher impossible. (ie, Clinical Trial NCT03618628 Title: 'Peak Plantar Pressures While Wearing a Carbon Fiber Off Loading Orthoses'. Primary outcome measure: 'plantar pressure during walking while the participant wears a brace orthotic based on the finite element (FE) model compared with (1) the brace orthotic based on current clinical standards and (2) barefoot'. Exclusion criteria: 'unable to ambulate and complete testing required for study participation' and 'severe foot deformity of the hindfoot or any deformity of the foot with a dislocation resulting in a bony prominence on the plantar/weight-bearing surface of the foot').
2. Relative exclusion criterion: a condition that, in relation to the primary objective of the study, made the evaluation by the researcher difficult but still possible using a different methodology. (ie, NCT01483625 Title: 'tiotropium (18 µg) in patients with COPD with a respiratory infection'. Primary outcome measure: 'through forced expiratory volume in 1 s after 12 weeks on study drug'. Exclusion criteria: 'visual impairment that as judged by the investigator does not allow the patient to independently read and complete the questionnaires and electronic diary (eDiary)').
3. Questionable exclusion criterion: a condition with no evident correlation with the primary purpose of the study (ie, NCT01952834 Title: 'effect of probiotic supplementation on endothelial function'. Primary outcome measure: 'brachial artery flow-mediated

dilation. Flow-mediated dilation is measured as the percent change in brachial artery diameter as measured by high-resolution ultrasound based on arterial diameter prior to and following 5 min flow occlusion to the forearm'. Exclusion criteria: 'known history of cognitive impairment or inability to follow study procedures'). All the explicit exclusion criteria that were considered as questionable were discussed by three researchers in order to arrive at a consensus on the assigned judgement. Where two or more explicit criteria for exclusion were present, judgement was expressed on the most exclusionary level. Any dubious or complex criteria noted by individual researchers were discussed collegially in order to reach a consensus.

Other exclusion criteria that could be correlated with disability in the form of comorbidities not otherwise specified, or other poorly defined criteria or generic expression allowing the researchers to include only participants they considered suitable for the study, were recorded as 'implicit exclusion criteria'. Implicit exclusion criteria were categorised as questionable by default, given the unclear and undetermined nature of the exclusion criteria.

Primary outcome measures were: (a) number of trials with at least one explicit exclusion criterion for PWDs and (b) number of trials with at least one implicit exclusion criteria. Secondary outcome measures were: (a) number of trials with an absolute exclusion criterion for PWDS; (b) number of trials with a relative exclusion criterion for PWDs and (c) number of trials with a questionable exclusion criterion for PWDs.

Data analysis

The data were analysed using mean, minimum and maximum and SD for the variable 'number of participants' (page 1, online supplemental material 1). For all other variables, that is, 'age of eligibility', type of trial ('pharmacological interventional trial', 'surgical interventional trial', 'non-pharmacological non-surgical interventional trial', 'diagnostic trial'), 'masking', 'inability to grant informed consent', 'explicit exclusion criteria', 'disability', 'physical impairment', 'cognitive impairment', 'behavioural or psychiatric disorders', 'communication or language impairment', 'sensory impairment: visual or hearing impairment', 'implicit inclusion criteria', 'absolute', 'relative' and 'questionable' (pages 2–21, online supplemental material 1), a frequencies computation was conducted. The percentages of explicit exclusion criteria were considered relative to the total number of trials with at least one explicit criterion.

Patient and public involvement

This study did not involve any patients.

RESULTS

Based on the search criteria, a total of 2809 trials were selected for the 10 selected disease categories. At a subsequent review, 99 trials were eliminated as they were repeated across categories resulting in a net total of 2710 trials with a total of 1 243 829 participants (Min. 1, Max. 94 321, mean 458 977). There were 170 (6.3%) paediatric-only studies, 2374 (87.6%) adult-only studies and 166 (6.1%) trials comprising subjects of all ages. Among the clinical trials reviewed, 1754 (64.7%) were pharmacological interventional trials, 64 (2.4%) were surgical, 759 (28%) were non-pharmacological non-surgical and 133 (4.9%) were diagnostic trials (figure 2). Any form of masking was present in 1499 of the trials (55.3%). 'Inability to grant informed consent' was present in 480 trials (17.7%). Explicit exclusion criteria were found in 958 trials (35.3%) with the disability categories most frequently excluded being 'behavioural or psychiatric disorders' present in 588 trials (61.4%) and 'cognitive

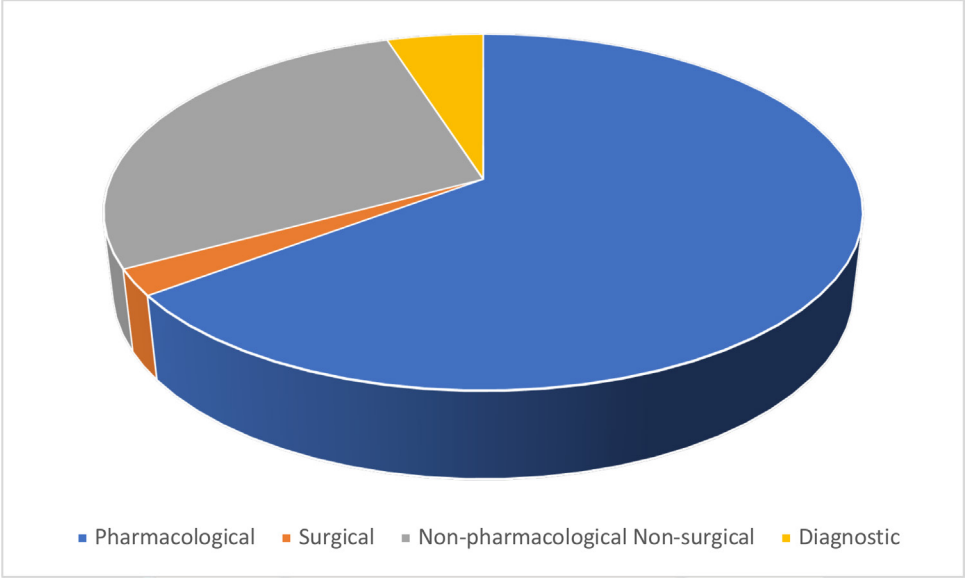

Figure 2 Types of clinical trials.

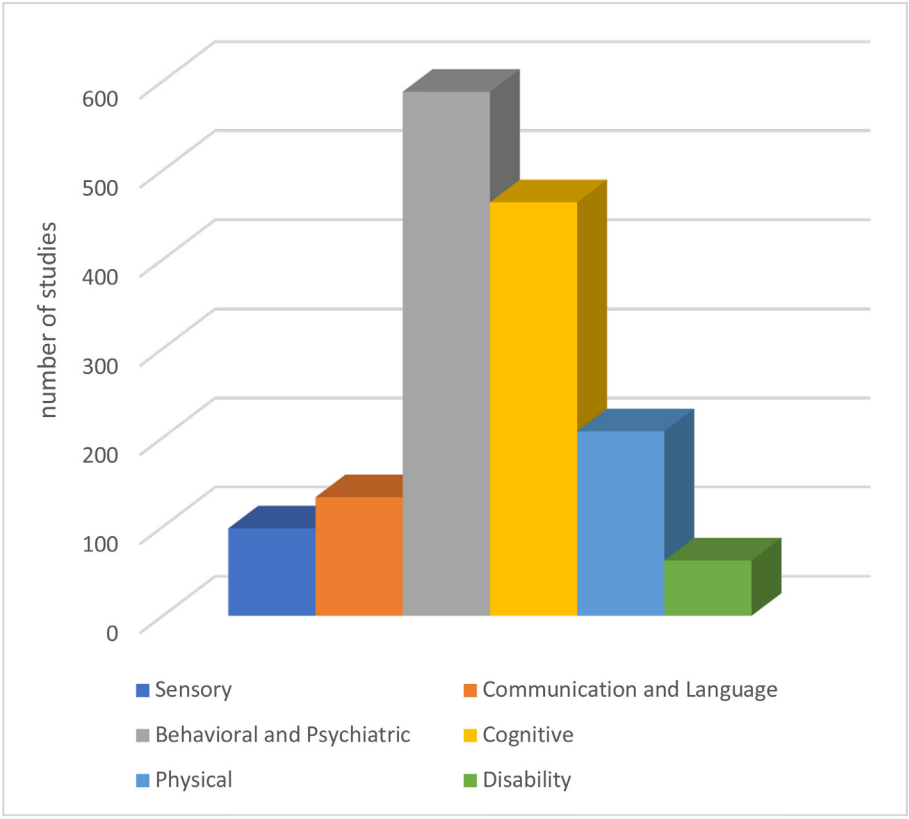

Figure 3 Categories of disabilities as explicit exclusion criteria.

impairment' present in 464 trials (48.4%) (figure 3). In relation to the primary aim of the respective clinical trials, a rating of congruence as 'absolute exclusion criterion' was given in 29 trials (3%). In 920 trials, (96%) the exclusion was considered 'relative'; the exclusion was considered 'questionable' in 9 trials (1%). The rating of congruence in the different subgroups of disabilities is reported in figure 4. Implicit exclusion criteria were present in 1205 trials (44.5%) and the rating assigned was 'questionable' by default.

DISCUSSION

The results of this study reveal a high rate (over 35%) of explicit exclusion of PWDS for one or more areas of health conditions and impairments associated with disability, from interventional clinical trials related to the first leading causes of DALY in males and females If other less defined exclusion criteria for disabilities are added the percentage of trials that could potentially exclude PWDs reaches almost 60%. Although these second exclusion criteria do not explicitly refer to PWDs but might include them, they could significantly increase the number of trials in which PWDs cannot participate.

There is a growing interest regarding the issue of the exclusion of PWDs from research. DeCormier Plosky *et al* recently published a study in which interventional protocols in four therapeutic areas were evaluated and found that the cause of such frequent exclusion of PWDs lies in eligibility criteria for clinical trials with 'broad, non-specific language and without explanation or rationale'.[7] The lack of inclusion of PWDS through rigid inclusion and exclusion criteria has been previously documented.[3] The reasons given to exclude PWDS from large-scale clinical research are partially related to the concern of a potential risk of abuse and exploitation; this applies to people with cognitive impairment and psychiatric disorders, in particular those who are unable to give informed consent.[17 18] Although the importance and the ethical value of informed consent in research studies are not questionable, the inability to provide consent by PWDs should not become an obstacle to their participation. According to the criteria given in the Additional Protocol on Human Rights and Biomedicine, concerning Biomedical Research Art 15, the research involving persons not able to consent to research is allowed if the following conditions are met: complete and exhaustive information is given to their legal guardians; the results of the research have the potential to produce a direct benefit to his/her health; the research cannot be carried out with the same effect on individuals capable of giving consent; the risks which may be incurred by the PWDs are not disproportionate to the potential benefits of the research. The same article states that research can be allowed with exception only if adhering to the above protective measures and if the research in question 'has the potential to benefit other persons afflicted with the same disease or disorder or having the same condition of the study participant'; and 'the research entails only minimal risk and minimal

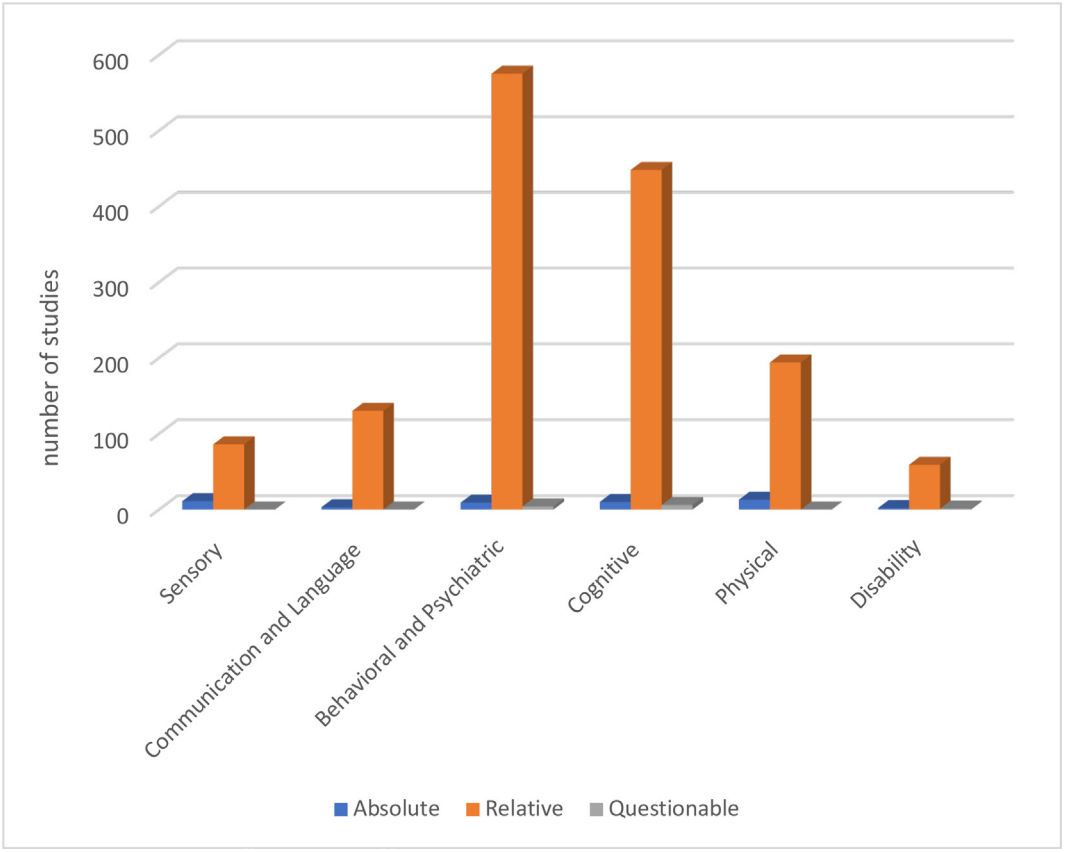

Figure 4 Rating of congruence of explicit exclusion criteria in relation to the primary aim of the analysed clinical trials.

burden for the individual concerned'.[20] Other reasons given for the exclusion of the same category of persons are the inability to follow instructions and collaborate in study procedures. Researchers may be concerned about 'compromising' the integrity of their research protocol by introducing confounding factors that might weaken the results of the research.[21] To this we might add a lack of knowledge and confidence in dealing with PWDs as well as a degree of 'cultural bias' and disrespectful attitudes towards PWDs.[22 23]

In our study, judgement of the appropriateness of the exclusion criteria was based on the feasibility of the study described in relation to the primary objective and the type of health conditions and impairments associated with disability presented by the excluded persons, and not on other types of ethical or moral judgements. It is worth noting the high percentage of trials with 'relative' exclusion criteria, meaning that the primary objective of the study could have been achieved through the adaptation of the study design for excluded PWDs. Behavioural or psychiatric disorders and cognitive impairment were the two main causes of exclusion from analysed clinical trials; the exclusion criteria in these categories were considered 'absolute' (absolute inability to participate in the study in relation to the primary objective) in only 1.5% and 2.2% of cases, respectively, and 'relative' in over 96% of the clinical trials. It is noteworthy that the term 'psychiatric disorders and cognitive impairment' comprise an extremely heterogeneous group of subjects both for type and severity of disorders that would require a better specification to define the actual risk or inability to participate in clinical trials. Although sensory exclusion criteria were rated as absolute more frequently compared with other exclusion criteria, the percentage of clinical trials with sensory exclusion criteria that were considered 'relative' was still remarkable. Some researchers may not be fully aware of the potential of people with sensory disabilities; for example, blind people can take advantage of available technology to perform tasks that usually require good vision (ie, filling out questionnaires).[24] Our review highlights that in more than 88% of the trials the exclusion of people with sensory deficits, in relation to the primary objective of the study, could have been avoided. In no case, however, was the exclusion of persons with sensory impairments found to be questionable.

Another way in which PWDS are excluded is the use of comorbidities as exclusion criteria.[6] There is a high correlation between chronic conditions and disability. In a population of US working-age adults (18–64 years), nearly 17% reported disabilities during a given year and the incidence of one or more chronic conditions was 45% when no limitations were reported, 80% when the limitations were not affecting IADLs/ADLs and nearly 90% when the limitations were affecting Instrumental activities of daily living/Activities of daily living (IADLs/ADLs). In the same population, 25% of the people with one or more chronic conditions reported any disability.[25] This suggests that the exclusion of people from research

due to the mere presence of comorbidities indirectly excludes the majority of PWDs.

In our study, the presence of generic or ill-defined exclusion criteria was as high as 44.5% of the clinical trials analysed, allowing the researchers to include only those participants considered suitable for the study. The attempt to select the best suitable population for specific research may limit the external validity of the study and the applicability of the results to the 'real-world' population.[15] Several concerns already exist and are highlighted in the literature regarding the exclusion of PWDS from mainstream research.[7] From a research perspective PWDs represent a large, heterogeneous subgroup that needs to be taken into consideration for both general health issues and their specific pathologies and needs; the exclusion of PWDs may weaken the external validity of research study results. Furthermore, without studies including PWDs, clinicians lack evidence of treatment applicability towards this large minority group determined to be effective in the general population.[6]

Besides scientific concerns regarding the exclusion of PWDS ethical and social issues arise deserving of additional consideration. The ethical principles of distributive justice, equity and beneficence in research need to be applied to all categories of people.[26] PWDs have the right to participate in research and benefit from study results, innovative therapies and precision medicine just as any other group of patients. Furthermore, PWDs have the right to participate in research not only as subjects but as active partners in the research process. The exclusion of PWDs from clinical research reflects the fact that they are often not considered as stakeholders or active contributors in the research agenda with the consequence that research protocols are not designed with appropriate accommodations to meet their specific needs, nor as beneficiaries of large-scale biomedical research.[24] It is time to move from an although laudable approach to public health aimed at denouncing disparities to the actual implementation of strategies focused on the concept of equity in health as the highest and most inclusive level of health possible.[27] A cultural shift towards the inclusion of PWDS in scientific research is needed. Accessible research designs could allow PWDs to participate fully in health-related research activities. This goal may be achieved through a 'universal design of research' model that does not require adaptation for people with special needs. Other studies may require 'accommodation' regarding how the task is accomplished, so that PWDs may also be able to actively participate in a task that they would otherwise be unable to complete. 'Modification' would instead require a further change in methodology in order to achieve the objectives of the research, using a different strategy.[4] Besides accessible research design for general health issues, precision medicine research (PMR) related to single pathologies affecting PWDs, particularly regarding rare diseases, is highly recommended. PWDs should be included in PMR in order to have equal access to innovative therapies.[28]

One of the limitations of this study is that we referred to the GBD 2017 in place of the more recent version 2019: between the two studies there is only one difference in the top 10, level 3, leading causes of global DALYs in both male and female lists. Another limitation is that all the trials analysed were selected from ClinicalTrials.gov; this may produce a bias due to the types of trials found in this database, characterised by a higher study design quality and well-formed inclusion and exclusion criteria as compared with unregistered trials. Exclusion and inclusion criteria were extracted from the database and not from the original study protocols which we suspect may be even more detailed regarding eligibility criteria.[13] Another limitation is that, due to the number of trials analysed, each subgroup of trials was analysed by a single researcher, though based on strictly predefined criteria. Judgement of questionable exclusion criteria was assigned only following discussion and consensus reached among three researchers; any other conflicting result was dealt with in a similar manner.

Among the strengths of our study is the large number of clinical trials analysed over an extended period of time. Furthermore, the choice to analyse trials regarding the 10 top leading causes of global DALYs, according to the GBD Study, highlights a perspective on medical issues with a strong impact on global health.

We believe that the exclusion of PWDs might reflect an attempt to protect them from abuse and exploitation, but it also may be a direct consequence of a research perspective that privileges the absence of confounding factors in order to reach a result as 'clean' as possible. The limitation of this research perspective is the lack of evidence-based clinical data regarding a large subgroup of the population compromising the appropriateness of diagnostic and therapeutic interventions. There is a need to sensitise and empower medical professionals at all levels as well as the research community regarding the care of PWDs, which would allow them access to diagnostic procedures and innovation therapies.

CONCLUSION

This study highlights that a large majority of clinical trials contained explicit and/or implicit exclusion criteria that directly or indirectly exclude PWDs. The consequences of such exclusion on medical knowledge and on clinical practice regarding PWDs are potentially serious and require more in-depth analysis.

Moreover, in most clinical trials, the exclusion of PWDs could have been avoided through a more inclusive study design or via adaptations, without compromising their overall quality. Much work needs to be done towards a feasible integration of PWDs into research.

Contributors The authors confirm contribution to the paper as follows: study conception and design: GC, OC and NM. data collection: GC, OC, CB and CT. Analysis and interpretation of results: GC, OC, AL, CT, CB, SC, NM and SE; draft manuscript preparation: GC, OC and SC. All contributing Authors reviewed the results and approved the final version of the manuscript and are aware of and

agree to the submission of this manuscript. All authors have read, and confirm that they meet, ICMJE criteria for authorship. Guarantor: GC.

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ORCID iD

Guido Camanni http://orcid.org/0000-0003-0881-5426

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