

Manuscript number: SSM-D-17-02601R1

**A systematic review of the methodological and practical challenges of undertaking randomised-controlled trials with cognitive disability populations**

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Acknowledgements: This project was funded by a Department of Education & Learning (DEL NI) grant (supporting PM). The funders had no input into the design, conducting or reporting of this systematic review.

Conflict of interests: There are no conflicts of interest noted by the authors.

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**(Word Count 14,992 in total)**

## **Abstract**

Approximately 10% of the world's population have a cognitive disability. Cognitive disabilities can have a profound impact on a person's social, cognitive or mental functioning, requiring high levels of costly health and social support. Therefore, it is imperative that interventions and services received are based upon a sound evidence-base. For many interventions for this population, this evidence-base does not yet exist and there is a need for more Randomised Controlled Trials (RCTs). The process of conducting RCTs with disabled populations is fraught with methodological challenges. We need a better understanding of these methodological barriers if the evidence-bases are to be developed. The purpose of this study was to explore the methodological and practical barriers to conducting trials with adults with cognitive disabilities. As a case example, the literature regarding RCTs for people with intellectual disabilities (ID) was used to highlight these pertinent issues. A systematic literature review was conducted of RCTs with adults with ID, published from 2000-2017. A total of 53 papers met the inclusion criteria and were reviewed. Some of the barriers reported were specific to the RCT methodology and others specific to people with disabilities. Notable barriers included; difficulties recruiting; obtaining consent; resistance to the use of control groups; engaging with carers, staff and stakeholders; the need to adapt interventions and resources to be disability-accessible; and staff turnover. Conducting RCTs with people with cognitive disabilities can be challenging, however with reasonable adjustments, many of these barriers can be overcome. Researchers are not maximising the sharing of their experience-base. As a result, the development of evidence-bases remains slow and the health inequities of people with disabilities will continue to grow. The importance of the MRC guidelines on process evaluations, together with implications for the dissemination of 'evidence-base' and 'experience-base' are discussed.

**Key words: barriers; randomised controlled trial; evaluation; cognitive disability; intellectual disability; evidence base; experience base**

## Introduction

Globally about 10% of the world's population, approximately 650 million people, live with a disability (UN Fact sheet on Persons with Disabilities), many of whom have a cognitive disability. Cognitive disability can have many causal factors (e.g. stroke, dementia, acquired-brain injury, autistic spectrum disorder, intellectual disability) and can arise at different stages of life. Although the list of disorders that feature cognitive impairment may seem diverse, there is significant overlap amongst disabilities in how impairment may impact on a person's quality of life and their ability to function independently. For example, disruption of family life, reduced social activities and social isolation are commonly experienced by people with various developmental, and acquired, cognitive disabilities including dementia, stroke and autism (Giebel et al., 2014; Northcott et al., 2016; Spain & Blainey, 2015).

A clear exemplar of a common cognitive disability is the case of people with intellectual disabilities (ID). ID is a class of disorders with a range of genetic, biological and psychosocial aetiologies. The two most commonly used systems for diagnosing an ID are the American Psychiatric Association's Diagnostic Statistical Manual (DSM) and the World Health Organisation's International Classification of Diseases (ICD). Traditionally ID was often diagnosed when a person's IQ fell below two standard deviation below the mean (i.e. <70). More recently DSM-V determines ID as being based more upon functioning level than IQ level. People with ID will have difficulties in intellectual functioning (such as problem-solving, planning, abstract thinking, reasoning, an IQ <70+/-5). They will also have difficulties in adaptive functioning (i.e. self-care, domestic skills, social skills, self-direction, community, academic skills, work, leisure, health and safety); all occurring during development. The World Health Organisation's ICD sees intellectual disability as "a group of developmental conditions

characterized by significant impairment of cognitive functions, which are associated with limitations of learning, adaptive behaviour and skills”, with IQ being only one clinical marker for helping to determine ‘severity’ of the disability – the ICD further classifies ID into mild, moderate, severe and profound, largely on the basis of IQ and functioning (Salvador-Carulla et al., 2011). Approximately 1%-2% of the world’s population have an ID, which amounts to about 15 million people in Europe alone (<http://www.euractiv.com/sections/health-consumers/people-intellectual-disabilities-eu-deserve-proper-healthcare-310015>); and it is predicted that this population will grow. Likewise, population growth with the other cognitive disability populations is also predicted. For example, the global prevalence of dementia is expected to double every twenty years (Mavrodaris et al., 2013).

Despite people with ID living longer (Braddock et al., 2013), recent research in the UK, Ireland, USA and Australia highlights that they are dying approximately 20 years earlier than non-ID peers from respiratory disease, coronary heart disease and specific cancers (Heslop et al., 2013; McCarron et al., 2015; Trollor et al., 2017; US Surgeons General Report, 2002). Furthermore, people with ID have higher prevalence rates of a range of secondary chronic health conditions (i.e. sensory problems, epilepsy, Type 2 diabetes, osteoporosis, mental health, dementia) compared to the non-ID population (Taggart & Cousins, 2014). Alongside this, there is growing international evidence to show that many of these health inequalities can be avoided with appropriate health surveillance, health screening, early interventions and effective clinical interventions (Emerson & Hatton, 2013; Heslop et al., 2013; Taggart & Cousins, 2014). An important distinction can be made then between the unavoidable health inequality faced by people with ID due to the genetic nature of their disability, and the avoidable health inequities that they face due to inappropriate, inadequate or absent provision of services and care.

The global costs of providing primary/secondary healthcare and social care for those with ID, and other cognitive disabilities, is estimated to cost countries a substantial proportion of their overall fiscal budgets and is becoming unsustainable (Pavolini & Ranci, 2008; Wimo & Prince, 2010). For example, in the UK, older adults with ID account for 0.15-0.25% of the population, however they receive up to 5% of the total personal care budget (Strydom et al., 2010). The National Audit Office Report (2017) for the Department of Health reports that in England £8 billion are spent providing services to people with ID. In the Netherlands ID expenditure accounted for 9% of the total healthcare expenditure (Polder et al., 2002). Given the austerity measures many countries face today, it is imperative that pharmacological and psycho-social interventions are both clinically effective and cost-effective (Robertson et al., 2015) and are supported by a strong evidence-base.

In the non-disabled population, the evidence-base for many pharmacological and psycho-social interventions is informed by large scale randomised control trials (RCTs) and systematic reviews/meta analyses. RCTs are widely considered the 'gold standard' for testing the effectiveness of treatment interventions. This is in part because RCTs offer levels of rigour that many other methodologies lack. The three central principles of the RCT methodology are Randomisation, Control and Trial or testing of an intervention (see Figure 1):

- **Randomisation:** a representative sample of the population is randomly assigned to either an intervention or a control group;
- **Control:** measures are taken to reduce the influence of extraneous variables to isolate and examine the effect of the intervention under investigation;

- **Trial:** a treatment or intervention is tested within a specified framework to assess its effectiveness and/or efficiency. This requires a well-defined, and adhered to, protocol; the use of appropriate outcome measures; and the use of appropriate statistical methods.

## INSERT FIGURE 1 HERE

At first glance, the RCT methodology may appear deceptively simple. However, each of the three central principles of an RCT has its own unique methodological and practical challenges and levels of complexity. This complexity is magnified when incorporating participants with cognitive and communication difficulties, such as those with dementia, stroke, autism or ID. It could be argued that the RCT methodology is well suited to trials that test the *efficacy* of pharmacological interventions, e.g. does molecule A have a better impact than molecule B ***under optimal conditions***. However, many researchers are less convinced that the methodology should be used to test the *effectiveness* of behavioural or psychological interventions, which are often effected by the myriad potential interactions between people ***under real-world conditions***. As Hallfors & Cho (2007) state:

*“We argue that research has followed too closely after the pharmaceutical and medical product research model, with reliance on small efficacy trials under optimal conditions. While efficacy trials may be appropriate for medical product testing, they are not the best method for behavioural intervention research. Real world feasibility testing is essential, and external validity must become as important as internal validity for evidence of effectiveness.”* (p244- 245)



Despite Hallfors & Cho's warning, there is still a heavy reliance in Evidence-Based Practice upon RCTs. A common occurrence in both systematic reviews and meta-analyses within the ID field is the statement that there is a dearth of evidence in the form of high quality RCTs (Koslowski et al., 2016; Sohanpal et al., 2007; Vereenoghe et al., 2013). As such, the development of evidence-bases within the ID field lags considerably behind the non-disabled fields (Hastings, 2013). RCTs in the ID field remain uncommon and many have been fraught with methodological and practical challenges, and shortcomings. Not only are disability-specific trials uncommon, but it has also been shown that many people with cognitive disabilities, and particularly ID, are routinely excluded from 'mainstream' clinical trials (Brooker et al., 2015). Feldman et al. (2014) in a review of 300 randomly chosen RCTs found that people with ID were included in only 2% of these studies: with over 90% automatically excluding people with ID. Common RCT exclusion criterion included: language difficulties and/or cognitive impairment or inability to follow the intervention protocol. This further highlights the negative attitudes and on-going discriminatory practices that people with ID face. If the evidence-base for pharmacological and psycho-social interventions for people with ID is to be developed, then clearly a way must be found to either facilitate the inclusion of people with cognitive disabilities in mainstream RCTs, or more disability-specific trials must be commissioned and funded.

Whilst the generation of evidence from RCTs and systematic reviews is important, so too is the appropriate sharing and reporting of this evidence. The CONSORT statement (Schulz et al., 2010) proposes best practice and standardises the reporting of RCTs to ensure that important information is presented in such a way that readers can use the information to inform their decision-making and could, if required, replicate the study. The CONSORT statement is a 25-item checklist focusing on how the trial was designed, conducted,

analysed, interpreted and has been adopted as a framework of best practice reporting in many peer reviewed journals across health and social care research fields. There are several variations of the CONSORT to accommodate different trial designs, interventions and data types (see <http://www.consort-statement.org/extensions>). Although frameworks such as CONSORT provide guidance on how to report on the '**procedure**' of a trial, they do not require reporting on the '**process**' of the trial. For example, authors are prompted to report the methodological steps undertaken in conducting the trial, and provide a measure of outcome but they are not encouraged to report the methodological and practical challenges encountered and how these were overcome. This has led some researchers to criticise previous evaluation paradigms, suggesting that they rely too heavily on effect sizes and focus too sharply and simplistically on "what works" and are, ironically, unsuitable to testing complex interventions (Pawson, 2013). As our understanding of RCT design and evaluation processes have evolved, some researchers have proposed the development of 'Realist RCT designs' which, if incorporating realist evaluation principles, can lead to a better understanding of '*what works, for whom and under what circumstances*' (Bonell et al., 2012).

In 2014 the Medical Research Council (MRC) produced guidelines on a framework for developing Process Evaluations of Complex Trials (Moore et al., 2015). The MRC guidelines encourage the reporting of the barriers and facilitators encountered whilst conducting a trial, within three key areas of focus: 1) Implementation; 2) Mechanisms of Impact and 3) Context. Within the MRC Guidelines, **Implementation** refers to the process through which the intervention was delivered and includes the following topics: infrastructure of the trial; management of resources and any adaptations or alterations made in order to enhance implementation; fidelity to the protocol; dosage levels used and how any were provided with the intervention. **Mechanisms of Impact** refers to the means by which the intervention had

effects, whether intended or unintended and a discussion regarding possible factors that may have influenced these effects. **Context** refers to a reporting of the range of external factors which may have influenced either the implementation of the intervention or the effects measured. The extent to which the MRC guidelines have been adopted and the extent of their impact on trials pedagogy is as yet unclear.

A few methodological papers have been published that identify some of the methodological and practical challenges encountered while conducting research and more specifically RCT trials with people with ID. Jacquemont et al. (2014) reported heterogeneity within Fragile X populations, a lack of sensitive outcome markers and a lack of sensitive biomarkers, as being major challenges in researching the impact of pharmacological interventions for Fragile X. Molinari et al. (2011) reported low rates of recruitment, challenges with engaging gatekeeper agencies and issues concerning coordinating and obtaining informed consent. Lennox et al. (2005) reported similar issues, noting complex organisational structures, difficulties in locating potential participants, staff work load and limitations placed by ethical requirements which prevented directly approaching potential participants, as being major barriers to effective research with this population.

Leeson & Tyrer (2013, p. 313), in a review of RCTs supported by the Health Technology Assessment (HTA) of the National Institute of Health Research within the UK (from 1993-2007) determined that excessive governance regulations and “unnecessary bureaucracy” in the National Health Service (NHS) were contributing barriers to recruiting on time and on target. Baskin et al. (1998) in a review of the barriers to obtaining consent in dementia research found the process of obtaining surrogate consent to be a major hindrance to the research process. Lennox et al. (2005) cited a survey of 42 researchers reported by Siegel

and Ellis in 1985, which suggested that difficulties in recruitment were related to challenges in obtaining consent and the reliance upon the goodwill of an organisation to help with recruitment.

Despite the development of legislative frameworks such as the Mental Capacity Act (2005), which supports adults with varying capacity to consent to participating in research, ethical research engagement with vulnerable populations remains challenging. Indeed, it appears there continues to exist varied approaches to ethical practices, depicting the absence of agreement, ingrained struggles with the need to both protect the vulnerable and enhance self-determination, and disparities in expertise and practices (McDonald & Kidney, 2012). Thirty-years after Siegel & Ellis's survey, it could be argued that the situation has changed little. Although much has improved in terms of attitudes towards people with ID, and there has been considerable improvements in research methodology, researchers in this field are still faced with the methodological hurdles of how to ethically obtain consent and the reliance on gatekeepers for recruitment access.

In summary, the methodological and practical challenges reported in the literature are a function of the complexity of the RCT methodology combined with the complexity of the population in question. For example, researchers conducting trials with non-disabled populations are generally able to directly approach and recruit potential participants, whilst researchers in the ID and other cognitive disability fields must recruit through a number of 'gate keepers'. This indirect process has a number of potential inherent barriers. People with ID, their carers or professional staff may not fully understand the principles or importance of randomisation and therefore any one of these 'gate keepers' may refuse consent to participation. People with cognitive or information processing difficulties may not

understand questions in outcome measures or may not be able to follow instructions fully. Equally, staff or carers that are busy may not have the time to ensure that information is provided accurately or fully. All of these factors can have major negative impacts on a study.

If more RCTs are to be successfully conducted with people with ID then researchers will need to have a better understanding of how the factors unique to people with cognitive disabilities interact with the complexities of the RCT methodology. Whilst the methodologically-based publications above are important and useful, to date there has been no systematic attempt to collate the range of methodological and practical challenges faced by researchers conducting RCTs with people with ID. The current review seeks to address this gap.

**Aim:** The aim of this study is to systematically collate the methodological and practical challenges reported by trialists conducting RCTs with adults with ID. This will be achieved by reviewing the ID-RCT literature over a seventeen-year period (from 2000-2017) and collating the various methodological and practical challenges reported, and solutions employed, by researchers. This report is presented in line with the PRISMA guidelines (Moher et al., 2009).

**Systematic Review questions:**

1. What are the methodological and practical challenges reported by researchers conducting pharmacological and psycho-social intervention RCTs with adults with ID?
2. What solutions have been reported in the literature for overcoming the methodological and practical challenges?

## **Methods**

*Protocol Registration:* A protocol for this review was submitted to, and accepted by, the PROSPERO Database (Registration number CRD42016044043).

### **Search strategy**

The electronic databases PubMed, PsychInfo, Medline and Scopus were searched. The search strategy was defined in Medline (see Figure 2) and equivalents were devised for the other databases. The main search terms included Intellectual Disability and Learning Disability (which is more often used within the UK) and Randomized Controlled Trials. International spelling differences such as 'ized' and 'ised', plurals, and common meshed terms (including the previously common term 'mental retardation') were automatically included in the Medline search. The electronic search was initially conducted in January 2016 and an updated search was conducted in December 2017.

**INSERT FIGURE 2 HERE**

### **Initial Inclusion & Exclusion Criterion**

Due to the possibility of selection bias, our intention was to have a wide pool of potential papers; therefore, at the initial search stage, all English-language articles published in peer-reviewed journals between 2000 and 2017 which reported the results of RCTs that tested interventions of any nature with people with ID were included. From this wide pool of potential papers, the inclusion/exclusion criterion were applied at the level of title and abstract.

Studies were **included** if they were published in English, in a peer reviewed journal and reported the results of a RCT with adults with ID.

### **Study Selection**

The results from the searches of the four databases (PubMed, Medline, PsychInfo, Scopus) yielded 8849 citations (see Figure 3). These were checked for duplicates which, when removed, reduced the number of citations to 5724. The primary reviewer (PM) then used a systematic approach to screen the 5724 citations for relevance at title and abstract level.

Each of the citations were categorized as follows: 1) non-human study, 2) human but not ID-related, 3) RCT but not ID-related, 4) ID-related but not RCT and 5) ID-related RCTs.

Category number 5 (ID-related RCTs) was further sub-classified by 1) the age category of participants, 2) whether the target population was people with ID, families, staff etc, 3) whether the intervention tested was pharmacological or non-pharmacological. Studies were included in the final stage of the review if they reported the results of a trial where adult participants with ID were randomized to either an intervention or control group. A total of 53 papers met the inclusion criterion (see table 1).

### **INSERT FIGURE 3 HERE**

### **Data extraction**

*Reviewer agreement:* The primary reviewer (PM) reviewed all the papers whilst LT and VC each independently reviewed 25% of the papers – thus 50% of the papers were cross reviewed by a second reviewer. Occurrences of disagreement were discussed throughout the review process. Given that there was a high degree of consistency between reviewers at

an interim stage of this review, it was agreed that a 50% rate of cross-check to ensure accuracy was sufficient. During the review process reviewers noted the reporting of methodological and practical challenges within the framework discussed below.

### **Data Extraction Framework**

As this is the first reported occurrence of a review of this kind, the review team were unable to find a published data extraction framework that met the specific needs of this review. Therefore, a bespoke data extraction form was devised based upon the CONSORT statement (a copy of which can be obtained from the first author). It should be noted that the papers were not assessed to see if they conformed to the CONSORT agreement as many of the studies appeared in the literature before the CONSORT agreement was established. It is also important to note that the papers were not assessed in terms of the quality of the studies or their respective reports, but rather they were reviewed to ascertain the reporting of methodological and practical barriers that were faced during the conducting of the trials. The following headings were used to structure the data extraction: General; Title & Abstract; Introduction; Project Planning pre-trial; Methods – trial design, settings, recruitment & samples, interventions, outcomes, analysis. Through the process of data extraction, a number of methodological and practical challenges emerged.

### **Results**

The results are reported as follows; firstly, the profile of the papers reviewed is presented. This is followed by the methodological challenges, and solutions, cited in the reports relating to the Randomisation, Control and Trial components of an RCT.

#### **Profile of papers reviewed**



A total of fifty-three papers met the inclusion criteria and were reviewed. Table 1 shows the primary foci of each of the papers included in this review.

INSERT TABLE 1 HERE

*Populations:* Of the 53 papers reviewed, eighteen (34%) focused on adults with Down Syndrome (DS) only and twenty-two focused (42%) on adults with ID (cause of the ID was not cited). Of the remaining papers, ten (19%) focused on Prader-Willi Syndrome, two (4%) on Fragile X syndrome and another one on adults with phenylketonuria and ID.

*Settings:* Thirty-two papers (61%) were conducted in community settings and seven (13%) were conducted within hospital or institutional settings. The remaining fourteen papers (26%) did not specify their trial settings.

*Interventions:* Twenty-six papers (49%) reported results from pharmacological trials whilst twenty-seven papers (51%) reported on trials that were non-pharmacological or behavioural. Pharmacological interventions included: vitamin (n= 2), antioxidant supplements (n=1), Donepezil (n=2), Gabapentine (n=1), Growth Hormone (n= 8), medication reduction (n=1), Memantine (n=3), mGluR5 Antagonist AFQ056 (n=1), Olanzapine (n= 1), Oxytocin (n=1), Rimonobant (n=1), cognitive training plus epigallocatechin-3-gallat (n=1), risperidone (n=1), antimicrobial photodynamic therapy (n=1), and Saproterin (n=1).

Behavioural interventions included: the use of a behavioural support team (n=1), exercise & walking (n= 14), cognitive behavioural therapy (n=2), relaxation (n=1), massage (n=1), and health promotion programs (n=7).

*Sample sizes:* The median sample size for the 53 papers was 46 participants (range 10-443). Nine papers had a sample of more than 150 participants (see Figure 4). The median sample size for the pharmacological papers was 46 (range 10-337) and the median sample size of the non-pharma papers was 46 (range 16-443) (See Figure 4).

*Geographical spread:* The trials in this review were conducted in twenty countries – the USA (9, 17%), Spain (7, 13%), England (6, 11%), Australia (4, 8%), Sweden (4, 8%), Netherlands (3, 6%), Scotland (3, 6%), Denmark (2, 4%), Portugal (2, 4%), S. Africa (2, 4%), Brazil (1), Canada (1), France (2, 4%), Hong Kong (1), Ireland (1), Italy (1), Japan (1), Korea (1), Norway (1), and Switzerland (1). It should be noted that some of the studies were multi-country trials. This list refers to the country of origin of the first author in each report.

**INSERT FIGURE 4 HERE**

## **Randomisation**

As noted above, one of the central principles of the RCT methodology is that the study sample is representative of the population under investigation. With generic studies, this implies being 'representative' of the general population. With ID trials, this principle refers to samples being representative of people with ID. The term ID includes a myriad of recognised causal factors and is commonly quantified as being Mild, Moderate or Severe/Profound (British Psychological Society, 2015). As such, obtaining a representative sample is not straight forward. Less straight forward also is the pathway through which researchers must go in order to approach potential participants (see Figure 5). This systematic, multi-layered recruitment pathway is common for other cognitive disability populations too.

## INSERT FIGURE 5 HERE

*Recruitment of potential samples:* Whilst 26 of the papers (49%) discussed determining a required sample size through power calculations, only 14 (26% of the total group) reported meeting their target sample size. It would appear from the results of this review that small samples are a common feature in ID RCTs (median sample size in this review was  $n=46$ ). For example, Kondoh et al. (2011) reported the findings of a trial investigating the effects of Donepezil on the daily functioning of people with Down Syndrome. They had eleven participants in the treatment group and ten in the control group. Five papers reviewed noted difficulties in recruiting adequate numbers of participants. Prasher et al. (2002) reported that they were aware that they would not meet their target of 30-35 participants per condition, within their available catchment area. Rather than beginning to engage with additional agencies from another area, they proceeded knowing that they were sacrificing statistical power. They did not report *why* they were unable to reach their recruitment target. Similarly, Feldman et al. (2016) reported recruiting 24 participants with ID to a health promotion trial and noted that the sample size was less than a power analysis suggested, although they did not specify their recruitment target. De la Torre et al. (2016) noted that they had originally intended to recruit individuals with Down Syndrome aged between 18 and 30 years but, due to recruitment problems, they widen their age requirement to 16-34 years.

Gagiano et al. (2005), in a study of Risperidone as a treatment for disruptive behaviours for adults with ID, had to pool the results from two separate trials, both of which experienced difficulties recruiting their required sample sizes. Ten investigators, located in three countries across two trials recruited a total of 77 participants. They did not specify how many participants were originally recruited for each of the two individual studies separately, nor did

they report the reasons for their difficulties in recruiting. It would appear that conducting multi-site studies with these populations is often necessary and prudent. Sano et al. (2016) in a study of the impact of vitamin E in aging with people with Down Syndrome recruited 337 across 21 sites and in 5 countries. However, even with such a wide study catchment, they still did not meet their power analysis target of 400 participants.

Tyrer et al. (2017) in a test of Nidotherapy used a cluster-randomised design. Part of their rationale for the cluster design was to reduce the risk of cross-contamination but also because they believed it would aid recruitment efforts. The Tyrer et al report was the only case where a positive impact on recruitment was cited as a reason for using a cluster design.

Crawford et al. (2001) in a study of Gabapentine and Lamotrigine, acknowledged that they did not meet their recruitment target. They recruited 109 participants from 44 sites and suggested that their difficulty recruiting the required sample size was mainly due to participants not being able to follow study procedures, thus highlighting the need to recruit “a key carer to complete the assessments on the patient’s behalf” (p.113) Crawford et al. did not specify which aspects of the study procedures the potential participants were able to follow given that 72% of their actual sample were unable to dress themselves, and 59% were unable to feed themselves, without supervision. Thirty-percent of their sample were also unable to communicate, and many could not give informed consent.

*Identification of potential samples:* Out of the fifty-three papers reviewed, none of the reports cited the *identification* of adequate numbers of participants as being a methodological challenge. This finding was unexpected and does not concur with Lennox et al. (2005) who

cited sample identification and recruitment as a major methodological barrier for the majority of ID research.

*Assessing & Obtaining Consent:* Only one study (Prasher et al., 2002) cited the process of assessing or obtaining consent as being a methodological challenge. Although Prasher et al. noted the challenge in their discussion section, they did not provide details of how it was a challenge nor how they overcame it. Forty-seven papers (89%) reported that consent was obtained, but provided little information about how. Commonly used phrases included “We obtained consent from the next of kin or another responsible adult as appropriate for the consent of adults without mental capacity participating in clinical trials” (Hanney et al., 2012, p.529); “Signed informed consent was obtained from all subjects or their legal guardians prior to inclusion” (Jorgensen et al., 2013, p.754); “Written informed consent was obtained from all their parents or legal representatives” (Rosety-Rodriguez et al., 2014, p.876; Rosety-Rodriguez et al., 2013, p.950) and Amore et al. (2011, p.212) stated that “A formal written consent was compiled. For those who were unable to do it by themselves [provide consent], it was given by their guardians.” Boer and Moss (2016, p.323) noted “The legal guardians of the participants gave consent for participation in the study”. They did not specify why they only sought proxy consent.

Only four studies (7.5%) elaborated upon their informed consent process (Feldman et al., 2016; Jacquemont et al., 2011; McDermott et al., 2012; Shields et al., 2015). During initial screening of suitability for inclusion, McDermott et al. (2012) used the Short Portable Mental Status Questionnaire (SPMSQ) as a measure of cognitive ability. If a potential participant correctly answered 4 of 10 questions then it was deemed that they had the ability to learn simple concepts and so proceeded to the next stages of consent where a researcher

discussed the nature of the study, was available to read the consent documents to participants, answered any questions and facilitated participants consulting with friends or family before participants signed the consent forms. Where a participant had a legal guardian, consent was obtained from the guardian.

Shields et al. (2015, p.117) described a three-stage process for assessing and obtaining consent: 1) the decision was made “In conjunction” with a next of kin as to whether the person with ID was able to provide consent, 2) where able, the person with ID provided written consent, 3) where the next of kin decided that the person with ID was not able to give consent directly, written consent was obtained from the next of kin and assent was sought from the person with ID”.

Feldman et al. (2016, p.280) obtained consent by “presenting information verbally using simple language and asking basic comprehension questions, witnessed by a trusted person of the participant’s choice who signed a statement affirming that the participant was not coerced”. This is the only occasion that we have found in the ID literature where the potential participant was specifically afforded the opportunity to choose who counter-signed the consent process.

Only two papers stipulated a rationale for not obtaining informed consent directly from the participants. Jacquemont et al. (2011) conducted a study of a MgluR5 Antagonist AFQ056 with thirty adults with Fragile X. They stated that because their participants belonged to the category of ‘incapacitated adults’ (their average mental age was assessed as being approximately 67-68 months), then written consent was obtained from their legal guardians. Similarly, Chan & Chien (2017, p.534) in an evaluation of the clinical efficacy of massage

therapy, noted that most of the potential participants were “not mentally fit to give consent” and so consent was sought from parents, next-of-kin or guardians.

*Use of Control Groups:* The use of a Control Group in an RCT is one of the most basic, yet most critical components of an RCT (Kinser & Robins, 2013) that is used to reduce bias and discriminate outcome due to the intervention versus outcome due to other factors. While not directly cited as a challenge or a barrier, Aronow & Hahn (2005) noted that their funders/sponsors did not want an untreated control group in the study and wanted both arms of the study to receive some form of intervention, although the rationale for this was not provided. Jahoda et al. (2017) in a study of the effectiveness of behavioural activation for depression, noted that their funders also did not want the comparator to be treatment as usual. In their study the ‘control’ group received an eight-session guided self-help intervention. Thus, the authors were only able to assess the effectiveness of their main intervention relative to the comparator intervention. However, as Jahoda and colleagues (p.917) point out, the absence of a control group may actually have aided recruitment as the prospect of being randomly allocated to ‘treatment as usual’ may have induced reluctance within the various gatekeepers. The insistence of the funders in these cases appears to be an exception rather than a common theme in the literature and begs the question of how often this type of insistence or negotiation occurs in trials but does not get noted in the published reports.

## **Control – Reducing the Impact of Extraneous variables**

One of the central ‘unique selling-points’ of the RCT methodology is its proposed ability to reduce bias (Attia, 2005), i.e. to eliminate the potential influence of extraneous variables and sources of variance which are separate from the effect of the intervention under investigation.

People with ID and other cognitive disability populations are often dependent upon a range of individuals such as family members, carers and professional staff for their daily and social interactions, and for participation in research studies. We propose that each of these individuals becomes a 'co-participant' in a research study and the consequential range of co-participants opens the trial to a huge range of potential extraneous biases. They also have the ability to affect identification and recruitment/retention levels, as well as the quality of the data obtained during an RCT (see Figure 6). As such, it is important for researchers to understand the role and influence of co-participants in both generic and disability-specific trials.

*Engaging participants & families:* Turk et al. (2010) in an evaluation of handheld health records, included adults with ID and their carers in most stages of the trial process. They noted their links with a local ID advocacy group, with a disability charity and they also reported employing four people with ID who they trained as researchers. Staff members from a local ID service were seconded to support the ID researchers. The ID researchers were members of the trial steering group, were involved in staff recruitment, piloting the measures and were also participants in the study. Melville et al. (2015) when designing a walking intervention trial collaborated with small groups of adults with ID and carers to help create draft resources, such as educational booklets, which were appropriate to the developmental level of the participants.

*Cross-condition Communication:* Melville et al. (2015) noted that due to social opportunities, and pre-existing relationships, amongst participants, there was a risk of participants sharing study details across intervention conditions and thus introducing a source of bias. To overcome this potential, they clustered the participants by residence, use of day-care centre



and by paid carer. The same strategy was also used by Tyrer et al. (2017). Their study was conducted across 20 care homes and they used a cluster-design, rather than individual randomisation, because of a) the risk of cross-contamination between residents of each home, b) homes are natural 'clusters' and c) the potential for improved recruitment.

*Systemic variables:* Three of the papers (5.7%) cited staff turnover as being a methodological challenge that impacted on the data collection. Lennox et al. (2010) in their health intervention trial noted that staff turnover, and participants changing GPs, had an impact on retention levels and missing data. The impact of high staff turnover upon data collection was also noted by Turk et al. (2010) and Harris et al. (2017). Although it could be argued that staff turnover can be a challenge for any study, it has long been acknowledged that carers of people with ID are exposed to high levels of stress, with resulting high levels of burn out (Felce et al., 1993). In the Turk et al. study, dropout levels for carers were nearly as high as that of the participants with ID, thus having an impact on the quality and quantity of data available for collection.

*Influence of other stakeholders:* None of the papers reviewed directly cited engagement with stakeholders as a methodological challenge. This finding was also in contradiction to Lennox et al. (2005) who found that the size and managerial complexity of a stakeholder agency posed direct challenges for researchers in terms of issues such as communication difficulties and staff work load.

Although not cited as a methodological challenge, twenty-three papers (43%) mentioned the various stakeholders that were involved in their respective studies. For example, Hanney et al. (2012) discussed the role of the funders in the development of the study protocol, their

attendance at meetings and the limits to their editorial input. They did not however provide any details on how they engaged with the participants, their families or carers. Only eight papers (15%) reported any detail of how they engaged with their respective stakeholders (Ahmed et al., 2000; Bergstrom et al., 2013; Feldman et al., 2016; Jahoda et al., 2017; Melville et al., 2015; Ptomey et al., 2017; Shields et al., 2015; Turk et al., 2010).

*Engaging staff:* To enhance the motivation of participants, Shields et al. (2015) recruited, trained and deployed undergraduate physiotherapy students to serve as exercise mentors for participants with Down Syndrome. Ahmed et al. (2000, p.42) enlisted clinical consultants to refer potential participants to the study, after which the “families, care staff and (where possible) potential participants were consulted, the nature of the study was explained and written consent to participate was sought”.

Bergstrom et al. (2013, p.3850) developed their health promotion intervention in partnership with “managers, caregivers, and The Swedish National Association for Persons with Intellectual Disability”. They used a range of strategies to improve engagement including meetings between stakeholders, training events and newsletters. Bergstrom and colleagues highlighted the importance of ensuring that data collection was not burdensome on staff. Feldman et al. (2016) reported providing a 3-hour orientation session to direct-care staff, supervisors and managers regarding the intervention program. Designated managers from each participating agency were also trained as trainers.

Ptomey et al. (2017) mailed/e-mailed information about their study to various organisational levels within their recruitment catchment area, which were then followed-up with personal visits. Study staff also made personal visits to potential participants and carers. In an

attempt to aid data collection, Ptomey et al. recruited parents, carers or other individuals to act as a 'study partner' for each participant. The study partners were given a \$50 gift card at data collection at 6, 12 and 18-month timepoints. Jahoda et al. (2017) also recruited a 'support person' for each participant. They reported that each of the therapists in their study received 1-2 days training in the delivery of their respective interventions, together with receiving ongoing supervision.

**INSERT FIGURE 6 HERE**

## **Trial**

The third central component of the RCT framework is that a defined intervention is provided, as designed, to an appropriately large sample and tested with accurate measures using appropriate statistical analysis. This poses two major challenges for trialists: firstly, ensuring protocol fidelity amongst a wide range of stakeholders and secondly, ensuring the collection and analysis of valid and reliable data. As noted above, people with ID are characterised by an IQ below 70 and with difficulties in adaptive functioning. People with ID and other cognitive disabilities, therefore, often have difficulties processing information, understanding complex ideas, and performing certain skills of daily living. This, coupled with the sometimes-changing support systems that people with disabilities may rely upon, means that maintaining protocol fidelity can be a major challenge.

The designing of an intervention program, and an appropriate outcome strategy, must take account of the perceptions, needs, abilities and disabilities of all the participants and 'co-participants', if the trial is to be concluded successfully. It would appear from this review that many of the interventions and outcome measures used have developed with non-disabled

populations and have required varying degrees of adaptation. Although this may prove challenging for researchers, it would appear from the review that this process of adaptation is both necessary and achievable.

***Intervention or Treatment Program to be tested:***

*Ability levels of participants:* Four papers (7.6%) reported issues concerning outcome measures and participant ability levels. The Melville et al. (2015) study reported that many of their participants found subjective questionnaires, which utilised visual analogue scales, to be confusing. Therefore, “to take account of the study population, the researcher read the IPAQ-S questions to participants with support from carers where needed” (p.4). Shields et al. (2015) also facilitated participant understanding by allowing a researcher to read questions where necessary. Aronow & Hahn (2005) reported similar findings (see section Communication and Cognitive Abilities above). Kondoh et al. (2011) suggested that many of the scales used when measuring quality of life with people with Alzheimer Disease are harder to use with Down Syndrome (DS) populations because the baseline cognitive ability levels of DS participants is much lower. Hoybye et al. (2005) reported that due to time constraints with a Prader-Willi population, a full cognitive assessment was not completed. They did not specify if the time constraint was of a practical nature or if it was concerned with the ability of the participants to focus for a specific length of time.

Ptomey et al. (2017) highlighted that participant ability levels are important not only in deciding outcome measures but also the delivery method of an intervention. They note, for example, that group interventions may not be an optimum medium for adults with ID due to the diverse range of cognitive, communication and social skills levels.

*Need to adjust programs:* It could be argued that in some circumstances, cognitive ability levels are unimportant in medical intervention trials where the participants are blinded to group allocation and where bio-medical outcomes are used. With psycho-social, educational, health promotion or behavioural change interventions, the ability levels of the participants may have a significant impact on their ability to fully participate in the study. Five studies (Aronow & Hahn, 2005; Harris et al., 2017; McDermott et al, 2012; Melville et al., 2015; Shields et al., 2008) reported how they adjusted or delivered their training in a way that attempted to be facilitative, given the reduced cognitive capacity of their participants.

McDermott et al. (2012, p.2) reported piloting and amending their intervention program's concepts and methods in an iterative fashion with "hundreds of participants" before conducting their RCT, although they did not provide specific details of which amendments were made.

Melville et al. (2015) described how they adapted a walking program originally designed for adults and older adults who were non-disabled. The number of behavioural change techniques were reduced and then adults with ID and/or their carers were consulted regarding various drafts of information resources, before producing an ID-specific version of the Walk Well program. They did not, however, specify which techniques they removed and for what reasons.

Shields et al. (2008) reported an adaptation of a progressive resistance exercise training program proposed by the American College of Sports Medicine. Shields et al. provided an adapted 10-week program. They did not provide specifics of how their program differed from

the mainstream version, but they did discuss how the duration of their program may not have been long enough for their ID population.

Aronow & Hahn (2005, p. 164) noted that modifying intervention programs for this population “would require considerable adaption of instruments, mostly to simplify language” to ensure that participants could understand the information and adhere to the recommendations of the study. Aronow et al. reported having to make changes to their interventions and assessment strategies throughout the life of their pilot study although they did not specify what was removed and what was added in this process. Similarly, Harris et al. (2017) noted that their ‘Take 5’ weight management program was modelled on a program used by another service and then adapted for adults with ID. They did not however state which components were adapted or why.

*Protocol Fidelity:* The need for participants, staff, and researchers to closely follow the trial protocol is paramount in an RCT. This may be a major challenge when participants have information processing or communication difficulties, or when there is a high staff turnover as noted by Turk et al. (2010) and Harris et al. (2017). Jacquemont et al. (2011) reported that cognitive or communication difficulties amongst participants or carers may have contributed towards dosing errors, highlighting the potential that such difficulties can impact on treatment fidelity within a study.

*Retention and Attrition:* Attrition in RCTs can be a significant source of bias and some journals will not publish RCTs that have an attrition rate of over 20% (Peterson et al., 2012). Retention and the completion of data gathering across all time points can be particularly challenging with ID-RCTs.

Three studies (5.7%) discussed difficulties with retention and missing data. Bergstrom et al. (2013) noted that although they had good retention levels (only one participant lost to follow-up), participants did not always want to provide data at each collection point. Other reasons for missing values were difficulties using pedometers with participants with extreme mobility problems, or with the participants having difficulty placing themselves on scales to weigh themselves. McDermott et al. (2012) reported participant drop-out as being a major challenge, citing reasons such as participants not wanting further home visits, choosing other activities over the data collection and not wearing equipment for long enough to provide meaningful data. McDermott et al. (2012) paid participants \$5 for each of their four collection points, although they propose that \$5 was not sufficient to achieve the level of motivation required for the amount of data that they were collecting. Hanney et al. (2012) noted that a number of participants chose not to provide data at some points but did not withdraw consent to continue, thus retaining sample size but having missing data.

In order to mitigate against the impact of participant drop out and staff turnover, Turk et al. (2010) used a combination of collecting data from both participants and carers.

As previously highlighted, McDermott et al. (2012) paid participants at data collection points and their experience illustrates the vital role that motivation has upon the recruitment and retention within a trial and this has a direct impact on the amount and quality of the data that is obtained. Therefore, how researchers engage with the various stakeholders of a trial is of crucial importance.

*Lack of ID-specific outcome measures:* Five papers (9%) noted a lack of ID-specific outcome measures as posing a challenge. In their investigation of Donepezil, Prasher et al. (2002)

highlighted a lack of previous research on Alzheimer's and DS to guide their choice of efficacy measures. They also cited a lack of measures for monitoring changes in intellectual functioning for people with DS and Alzheimer's. Tauber et al. (2011), in their investigation of Oxytocin with people with Prader-Willi syndrome, noted that there were no previously published observational measures for their behaviours of interest, so they developed their own in-house observation grid. Sode-Carlsen et al. (2012) investigated the impact of growth hormone with people with Prader-Willi syndrome. They adjusted a physical activity battery proposed by Guralnik et al, (1994), designed to be a predictor of disability in non-ID 70+ year olds, by adding an additional 10m walking test. In their discussion, Sode-Carlsen et al. acknowledge that their tests were not strenuous enough for their population, by inference they had ceiling effects and the measures were not sensitive enough to change. De la Torre et al. (2016) noted that there is not an agreed 'gold standard' for cognition in adults with ID, so they assessed domains known to be impaired using sub-tests of commonly used mainstream tests, e.g. the Wechsler Adult Intelligence Scale-III. In four of the sub-tests used it was considered that the tests were too complex for adults with an ID so the child versions of the four tests were used instead.

Jorgensen et al. (2013) discussed the use of the Body Mass Density (BMD) and its appropriateness for people with Prader-Willi syndrome. The standard scoring of BMD is related to the patient's height. People with Prader-Willi often have a shorter than usual stature and therefore the standard calculation for BMD would give an inaccurate measure. Using physiological measures based upon population norms may not always be appropriate with populations who exhibit unique physiological profiles, such as height or weight, outside of the non-disabled norms.



*Adaptations of measures & scoring:* Five papers (9%) reported adapting existing measures or scoring mechanisms to meet the needs/abilities of participants. Jorgensen et al. (2013) adjusted the standard method of obtaining a BMD for use with people with Prader-Willi Syndrome. Melville et al. (2015) used facial expressions rather than word-based rating scales (see the first section in the results section on adaptations). For measuring physical activity levels, they used technologies such as accelerometers, which were found to be useful alternatives to manually creating written logs of activity levels. Kondoh et al. (2011) used an abridged version of International Classification of Functioning, Disability and Health (ICF) scales, previously validated in a number of settings and with people with DS.

Boada et al. (2012) used cognitive test scores based upon the mental age of the participants rather than their chronological age. Given that they were looking for changes in ability across time, they used raw scores rather than non-disabled normed scores because they believed that raw scores would not produce ceiling effects. Boada et al. used a test called the California Verbal Learning Test (CVLT-II) which has 16 items, but they changed to the 9-item short version after responses from their first participant highlighted that the longer version was not appropriate.

Aronow & Hahn (2005) used language appropriate for 'fourth grade' level (age 9-10 years) with their outcome measures. They changed the rating options in their interview schedules to include facial expressions rather than a word-based rating scale or a linear visual analogue scale. Although Aronow et al. reported progressively adapting their measures and intervention throughout the course of their study, unfortunately, they only described changes made to the assessments and did not provide information regarding changes to the actual intervention.

*Use of Non-ID Measures:* Lott et al. (2011) used a combination of ID-specific and generic questionnaires. They employed the Dementia Questionnaire for Mentally Retarded Persons (DMR), the Severe Impairment Battery (SIB), the Bristol Activities of Daily Living Scale (BADLS), The Brief Praxis Test (BPT) and the Vineland Adaptive Behaviour Scales (VABS). Turk et al. (2010) used a number of assessment tools, some of which were as yet unvalidated, while some were developed outside the ID field, and others were ID-specific. Tauber et al. (2011) developed an 'in-house' measure and incorporated Theory of Mind (TOM) tests from the Autistic Spectrum Disorder literature.

*Improving quality and validity of data:* To address the potential impact of stress levels on data provision, Boada et al. (2012) helped reduce anxiety levels of participants before data collection by having the researcher engaged in light conversation for a few moments at the start of each data collection session. Feldman et al. (2016) ensured that participants were offered a beverage and reassured that they could have a break at any stage. Prasher et al. (2002) sought to address general anxiety about study participation by providing 24-hour access to a consultation service to reduce participant or carer concerns about the medications being tested.

To maximise the accuracy and quality of the data obtained during a trial, it is sometimes essential that researchers find creative ways to accommodate participants' ability/disability levels as well as reduce levels of burden engendered by the data collection process. One paper reported a creative use of technology for recording food intake. Bergstrom et al. (2013) used digital photographs to log food intake rather than traditional food diaries. The photos automatically logged the date and time that the photo was taken. After submission, a

nutritional expert assessed the photos in terms of food diversity, vegetable consumption and intervention compliance.

Chan & Chien (2017) noted that, due to the poor cognitive and communication skills of their participants, the use of self-reported data would be 'inappropriate' and so they relied upon staff-reported observational measures.

## **Discussion**

Conducting RCTs can be a complex endeavour and this complexity is increased when including participants with cognitive disabilities. People with cognitive disabilities such as dementia, stroke, autism or ID are often directly or indirectly excluded from mainstream RCTs. At the same time, it is widely acknowledged that there is a lack of an evidence-base for many of the interventions received by these populations and more RCTs are urgently needed. This review is the first systematic attempt to collate the various challenges and solutions reported in the ID-RCT literature at an international level. Whilst the literature reviewed is specific to adults with ID, we propose that the challenges and solutions are common to many trials where the participants have various cognitive or communication disabilities. The review included 53 papers, both pharmacological and non-pharmacological RCTs, with adults with ID spanning a seventeen-year period from twenty countries.

Contrary to expectation (Lennox et al., 2005), few of the papers reviewed directly cited the identification and recruitment of an adequately sized and representative sample as presenting a methodological or practical challenge. However, based upon the sample sizes of the papers reviewed, recruitment of people with cognitive disabilities does in deed appear to be challenging. Seventy-seven percent of the papers reviewed had a total sample size of

less than 100 and 68% had a sample of less than 70. Half of the papers (27, 51%) did not discuss power analysis requirements and the majority of the papers reviewed did not discuss why their samples were small.

The specific reasons for the small samples within this review are not reported as they were not discussed in the trial publications. Sample sizes in this review are consistent with those reported in other systematic reviews (Spanos et al., 2013). The diverse range of factors that can cause a cognitive or ID, coupled with the huge variance in ability levels within these populations, means that it is possible that this field simply has too many 'specialised' categories and large representative samples are therefore not possible. This may be especially true with the pharmacological trials where the effect mechanisms of certain drugs may vary across different genetic disorders thereby necessitating highly specific samples. This can pose major time and cost-related challenges in identifying and recruiting adequate numbers of participants. On the other hand, it may be that behavioural change trials or health promotion interventions can be targeted at 'wider', less specialised populations and therefore can access a wider recruitment base, with resulting larger samples. In order to achieve usable sample sizes, multi-centre and often multi-country, studies appear to be the necessary norm for trials with this target population. Of course, this may add additional time for planning and recruitment, complexity in terms of governance structures and ethics applications, as well as increased costs. However, we believe that both researchers and funders should see this as a cost-effective investment in the long-term pursuit of addressing the significant health inequalities, and the prevalence of premature death, often experienced by people with ID.

What is clear from this review is that participants with cognitive disabilities often experience very high levels of dependence upon a wide range of sources for social and functional support. In some of the trials, levels of dependence were such that participants required support for eating and getting dressed, while others needed support for travel. This means that although living with increased choice in their daily lives, people with ID are not always living as fully autonomous individuals. Within research structures, people with disabilities are deemed vulnerable adults and an additional number of safeguards are placed around their identification and recruitment to research studies: in most instances researchers are not permitted to recruit potential participants directly and must instead recruit through a series of 'gatekeepers' such as statutory or voluntary agencies or family carers. The inability to recruit directly can have a serious limiting impact on recruitment (Cleaver et al., 2010). For trialists, this means that to recruit a certain number of individuals with cognitive disabilities, in real terms they must recruit from a much larger number of 'co-participants' (e.g. family carers, support staff, professional staff, agency management etc), each requiring additional time and resources to recruit. Each of these gatekeepers and 'co-participants' has the potential to introduce a myriad of sources of bias into the study, effecting recruitment, retention and data collection. Researchers require creative and robust mechanisms to recruit and retain this complex network of 'co-participants'. In addition to increased time, such activities may also require additional funding.

Creativity is also required in ensuring that psycho-social, educational and behavioural intervention programs and outcome measures are presented in ways that are accessible and easily understood by the participants and 'co-participants' in the study. Intervention programs originally designed for non-disabled populations will often require adaptation by reducing the complexity of the intervention, reducing the number of components in the intervention, and by

simplifying the language used throughout. If the process and details of such adaptations were to be better detailed in the literature, then other researchers could benefit greatly from the learning experiences of those who have trodden before them. Some of the studies in the review included potential participants and carers in the program adaptation process. We believe that as well as being a model of good practice, this is also more likely to lead to increased content validity, less missing and better quality data, better retention rates and program fidelity.

Whether for instructional use, as part of the intervention itself, or as part of the outcome measures used in the data collection, we propose that any language used should be strategically adapted to match the varying ability levels of the participants. This may necessitate different versions of resources being developed. Failure to match information resources to the various ability levels of participants and 'co-participants' can be detrimental to recruitment efforts. The use of ability-level norms rather than age-related norms being used with outcome measures is another important strategy for researchers to avoid floor effects with cognitively disabled populations. Another important, and related, point raised in this review is the lack of disability-specific outcome measures. The paucity of appropriate outcome measures potentially has serious implications for future research – the use of scarce research funding for projects that use invalid outcomes is hard to justify on ethical or financial grounds. Both researchers and funders need to divert time, energy and resources into testing and developing valid and reliable outcome measures. The number of ID and other cognitive disability trials has seen an increase in the past few years and there is now an urgent need to address this paucity of measures.

It would appear that many of the studies reviewed had good retention rates however many suffered from incomplete data. Reasons for this included: participants choosing not to provide data on a given occasion, and staff turnover, leading to missed data collection. Some researchers have attempted to overcome this challenge by using multi-source data collection. Others have embraced technology (such as taking digital photographs of plates of food - see Bergstrom et al., 2013) and are seeking innovative ways to ensure accurate data collection. It may well be that in the future, apps on phones will interact with participants to remind them and aid them in providing data.

As noted above, a number of challenges did not appear in the papers reviewed that may have been expected, as per previous methodologically-based papers. Previous literature has suggested that the identification and recruitment of potential participants, agency complexity (Lennox et al., 2005), challenges obtaining ethical approval, and staff attitudes are major challenges for researchers in this field (Oliver-Africano et al., 2010). These issues were not cited in the papers in this review and it begs the question 'why not?' Is it possible that researchers are experiencing more barriers but are not reporting them? Is it the case that researchers in this field are so used to facing such challenges that they are considered commonplace and not worth reporting upon, or are there other factors limiting which barriers and issues that get included in the RCT publications? Future reviews of the barriers in this area could address this question.

With the challenges entailed in obtaining 'representative' samples large enough to provide adequate power, and the complex sources of extraneous bias inherent with this population at large, it is worth asking if the RCT methodology, as it is currently espoused, is a cost-effective way to build the much-needed evidence-bases for this population. With highly

specialised trials, such as testing medications, then RCTs may well be the methodology of choice to ascertain the *efficacy* of the medication. However, when it comes to testing *effectiveness*, the majority of trials within this field struggled to recruit enough participants to achieve adequate power. Either researchers need to employ more creative ways to recruit, or they need to redefine how they determine power requirements, or they need to look at adaptations to the RCT methodology such as trials with small Ns combined into meta-analyses. The use of the RCT methodology employed with people with cognitive and intellectual disabilities is in the early stages of development and its continued growth, evolution and adaptation is to be encouraged. It may be anticipated that the cost per participant recruited will be greater than for the non-ID population, with a consequential impact upon funding for the research. This has significant consequences for all funders internationally.

A series of guidelines to support researchers to plan, develop and report upon high quality trials have been developed. The Medical Research Council (MRC) has developed guidelines on trial development (see Craig et al., 2008); the CONSORT statement provides guidance on how to report trial outcomes; and the MRC guidelines on conducting Process Evaluations (Moore et al., 2015)). Whilst CONSORT provides a framework for reporting WHAT happened during a trial and What were the OUTCOMES, the MRC Process Evaluation guidelines advise on reporting HOW the trial was conducted and in particular, what barriers the trialists faced and how they overcame them. Thus, it appears that our understanding of the process of evaluation through clinical trials is evolving. CONSORT encourages the sharing of the trials' 'evidence-base' whilst the MRC Process Evaluation guidelines encourage the sharing of the trialists' 'experience-base' (see Figure 7).



## **INSERT FIGURE 7 HERE**

While the field of disability-based RCTs is in its relative infancy, we propose that the sharing of the 'experience-base' is fundamental to the speedy growth of an 'evidence-base', and is equally vital. If this 'experience-base' is to be shared in a meaningful way then process evaluations must become a standard component within a trial design and authors and editors must encourage the publication of process evaluations as a valid scientific activity. To the best of our knowledge, only one of the studies included in this review has published a structured Process Evaluation of their trial, as per the MRC framework (the Melville et al., 2015 study – see Matthews et al., 2016). It is acknowledged that it is possible that process reviews of trials may not be included in trial reports due to the word restrictions placed by journals. If this situation is to improve then it is important that both trial funders and editorial boards of journals encourage the speedy adaptation of the MRC Process Evaluation guidelines and promote the idea that the reporting of process evaluations is a valuable addition to scientific knowledge. We believe that the sharing of this 'experience-base' will in time lead to: more robustly planned funding proposals, increased levels of user co-production, improved rates of recruitment & retention, better quality data collected, an increase in 'evidence-base', an increase in the standards of 'best practice', and ultimately it will contribute towards the reduction in the health inequalities experienced by people with disabilities.

## **Limitations of the review**

This review has a number of limitations. Firstly, it is limited to trials published in English. Secondly, it was noted in the review selection process that many papers did not specify in the titles or abstracts important details, such as the age groups of participants, trial setting (community versus non-community), and the methodology employed (i.e. RCT). Thus, there is a risk that a number of appropriate studies did not meet the inclusion criterion, although this is a potential shortcoming of any systematic review.

### **Strengths of the review**

This is the first systematic review of methodological and practical challenges relating to conducting RCTs in the ID field. The trials included in the review span seventeen years and twenty countries. Papers reviewed included psychopharmacology and psycho-behavioural across a range of disorders. The evidence-base for the management of those with ID is relatively sparse, however the past few years have seen a marked increase in the number of pilot and feasibility studies being published. It is likely that the number of full trials being conducted will also increase and this review is timely in helping to illuminate this subject and help inform researchers of the potential barriers that they may face, as well as possible ways to make adaptations to their trial designs.

### **Conclusion**

It is widely acknowledged that there is not yet a robust evidence-base for many of the interventions provided to people with cognitive disabilities, that their needs are often complex and the effect mechanisms for many interventions may be different than for non-disabled populations. There is a common call for more robust RCTs within this field. This systematic review provides insight into the range of methodological and practical challenges faced by researchers whilst conducting RCTs with adults with cognitive disabilities, and specifically

with ID. The results indicate that whilst there are a number of challenges unique to this population, with creative adaptations to intervention programs and outcome measures, the inclusion of people with cognitive disabilities into RCTs is very possible – arguably, it is also an ethical and moral necessity (Article, 19 & 26, UN Rights of the Person with Disabilities, 2006).

If people with cognitive disabilities are to be included into mainstream trials, or if more disability-specific trials are to be completed, then further exploration of the practical and methodological challenges encountered when conducting RCTs with people with cognitive disabilities is required. To enable appropriate and “reasonable adjustments” to be made, trials will probably require relatively higher levels of funding per person recruited than for trials with a non-ID population. If trialists are to develop the evidence-base that is urgently required, then they will also need to enhance the sharing of their ‘experience-base’. For this to happen, authors and editors need to encourage the reporting of the ‘experience-base’ within the trials literature. Process Evaluations, as described in the MRC Guidelines may be an important component of sharing knowledge and the development of a robust evidence base.

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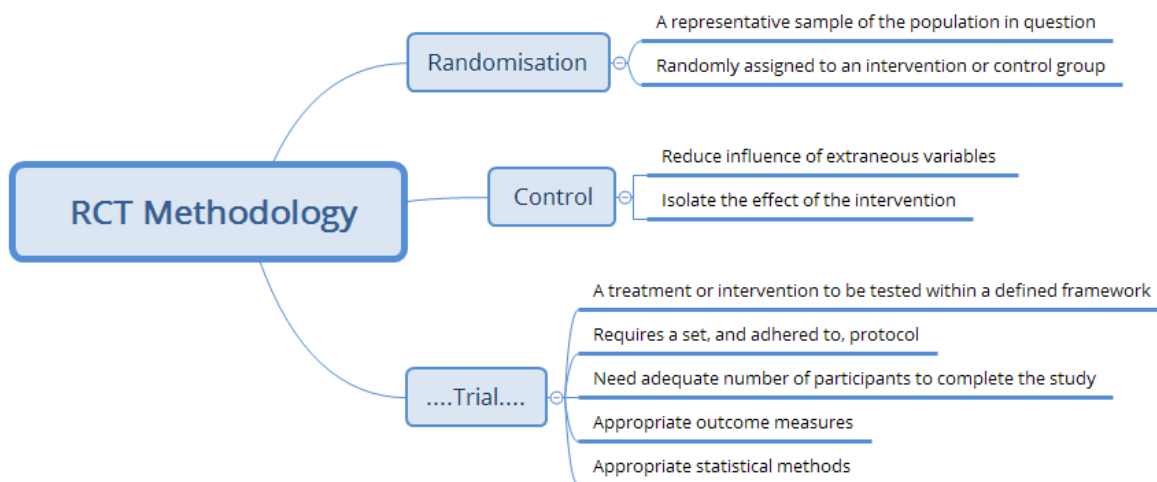
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**Figure 1: Central Principles of the RCT Methodology**

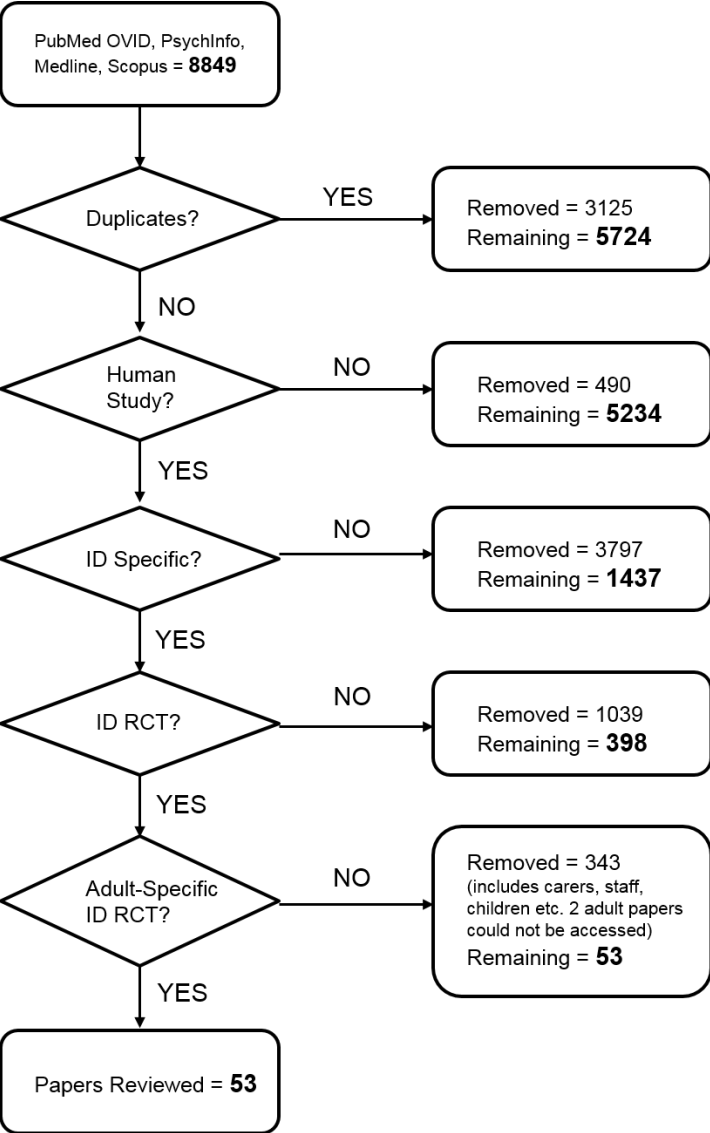


**FIGURE 2: Search strategy/terms used with Medline**

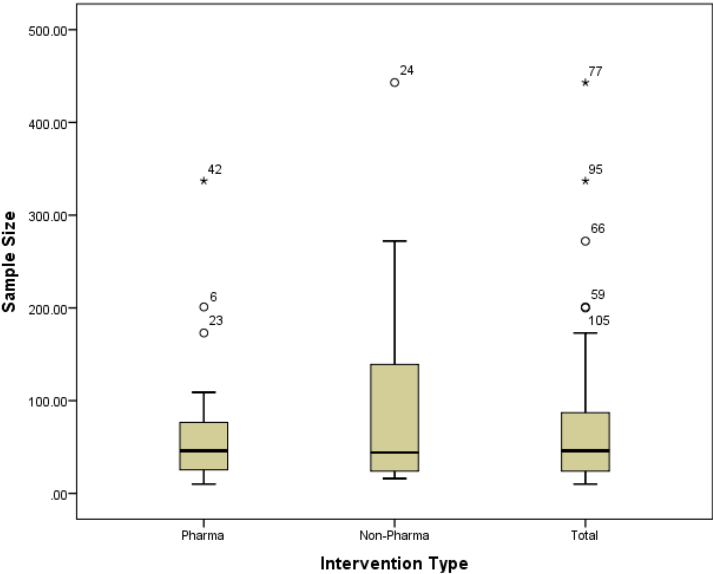
1. exp Intellectual Disability/
2. Learning Disorders/
3. ((mental\$ or intell\$) adj3 (impair\$ or retard\$ or disab\$ or defici\$ or handicap\$ or subnormal\$ or sub-normal\$ or "below normal" or "below average")).tw.
4. (learning\$ adj3 (impair\$ or disab\$)).tw.
5. 1 or 2 or 3 or 4
6. exp Randomized Controlled Trial/
7. random\$.tw.
8. 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. 5 and 10
12. limit 11 to yr="2000 - 2015"



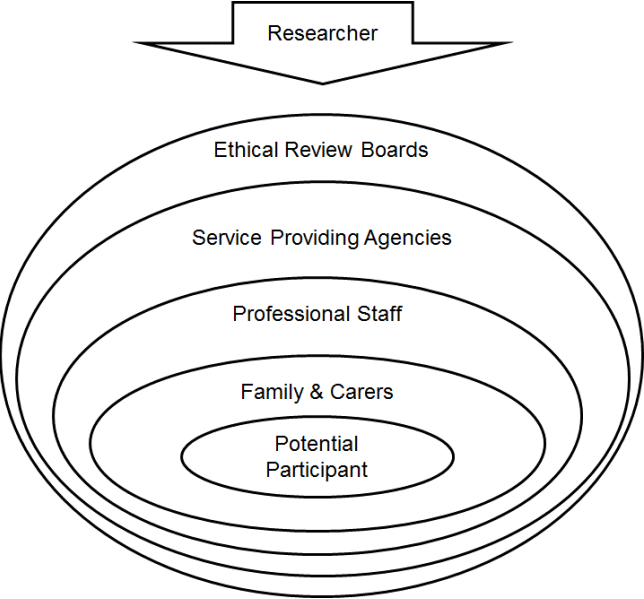
**Figure 3: Flow diagram of systematic review paper selection process.**



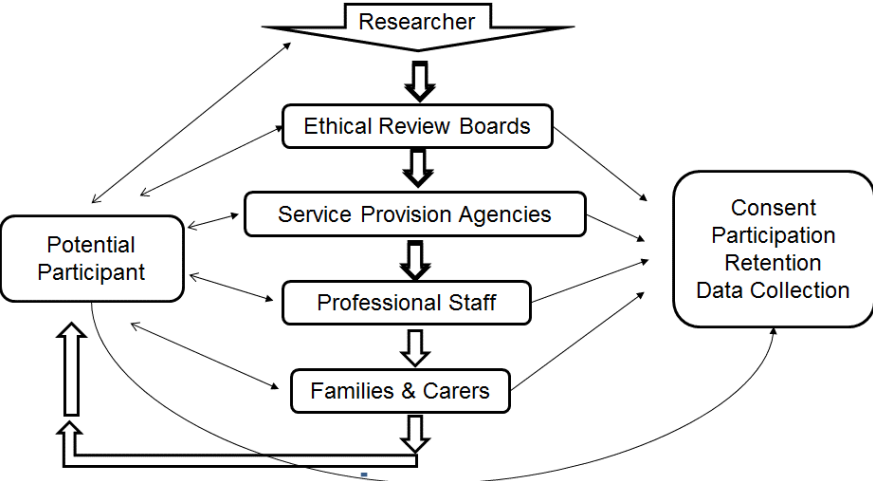
**Figure 4: Sample sizes of the pharmacological and non-pharmacological trials**



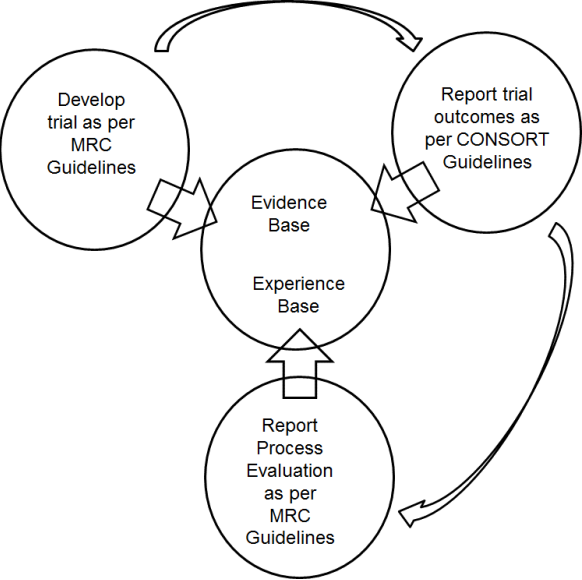
**Figure 5: Typical Gatekeeping pathway for recruitment**



**Figure 6: Various sources of influence and bias amongst trial stakeholders**



**Figure 7: The sharing of evidence base and experience base**



**Table 1: Primary foci of the papers included in the review**

<b>Authors</b>	<b>Year</b>	<b>Setting</b>	<b>Population</b>	<b>Intervention</b>	<b>Target</b>	<b>Sample size</b>	<b>N per condition</b>
Ahmed et al.	2000	Community	Intellectual Disability	Medication reduction	Reducing rates of anti-psychotic medication	56	C20, T36
Crawford et al.	2001	Community	Intellectual Disability	Gabapentin & lamotrigine	Epilepsy	109	T <sub>1</sub> 39, T <sub>2</sub> 44*
Prasher et al.	2002	Not clear	Downs & Alzheimer's	Donepezil	Dementia symptomatology and functioning.	31	C15, T16
Hoybye et al.	2003	Not clear	Prader-Willi	Growth Hormone	Body composition	17	C8, T9
Hoybye et al.	2004	Not clear	Prader-Willi	Growth Hormone	Serum adiponectin levels.	76	C59, T17***
Aronow, H. U. & Hahn, J. E.	2005	Community	Intellectual Disability	Health Promotion	Reduce health risks and improve health outcomes.	201	APN101, HRA100 ****
Gagiano et al.	2005	Not clear	Intellectual Disability	Risperidone	Disruptive Behaviours	77	C38, T39
Hoybye et al.	2005	Not clear	Prader-Willi	Growth Hormone	Cognitive, emotional, physical and social effects.	19	C9, T10
Zubillaga et al.	2006	Community	Down Syndrome	Vitamin D and calcium supplement	Bone metabolism	23	C11, T12
Levy et al.	2007	Not clear	phenylketonuria	Sapropterin for the reduction of phenylalanine	Reduction of phenylalanine	89	C47 T42

Shields et al.	2008	Community	Down Syndrome	Strength training	Muscle strength and physical functioning	20	C11, T9
Hassiotis et al.	2009	Community	Intellectual Disability	Behavioural Support Team service provision	Challenging Behaviour	63	C31 T32
Lennox et al.	2010	Community	Intellectual Disability	Health Promotion – use of health review tool and health diary.	Improved health intervention uptake and disease identification.	272	UC77 , ASK57, CHAP61, CA77***
Sode-Carlsen et al.	2010	Community	Prader-Willi	Growth Hormone	Body Composition	46	C22, T24
Turk et al.	2010	Community	Intellectual Disability	Health Promotion – personal health records	GP visits	56	C20, T36
Amore et al.	2011	Hospital / Institution	Intellectual Disability	Olanzapine vs, Risperidone	Aggressive behaviours.	62	O31, R31
Jacquemont et al.	2011	Not clear	Fragile X	mGluR5 Antagonist AFQ056	Behaviour	30	C14, T16
Kondoh et al.	2011	Institutional homes	Down Syndrome	Donepezil	Cognitive functioning	21	C10, T11
Lott et al.	2011	Community	Down Syndrome & Dementia	Antioxidant supplementation	Dementia	53	C26, T27
Motaghedi et al.	2011	Community	Prader-Willi	Rimonobant	Obesity	10	C4, T6**
Tauber et al.	2011	Hospital	Prader-Willi	Oxytocin	Disruptive behaviours	24	C12, T12
Boada et al.	2012	Not clear	Down Syndrome	Memantine	Cognitive and adaptive functioning.	40	C20, T20
Hanney et al.	2012	Not clear	Down Syndrome	Memantine	Cognitive impairment and Dementia	173	C85, T88

McDermott et al.	2012	Community	Intellectual Disability	Health Promotion program	Nutrition, Exercise, Stress, Communication	443	C216, T216
Sode-Carlsen et al.	2012	Community	Prader-Willi	Growth Hormone	Body Composition, Glucose and lipid metabolism.	46	C22, T24
Bergstrom et al.	2013	Community	Intellectual Disability	Health Promotion program	Diet and physical activity.	139	C66, T73
Jorgensen et al.	2013	Not clear	Prader-Willi	Growth Hormone	Bone Mineral Density	42	
Rosety-Rodriguez et al.	2013	Community	Down Syndrome	Resistance circuit training	Low-grade systemic inflammation	40	C16, T24
Shields et al.	2013	Community	Down Syndrome	Strength training	Muscle strength and physical activity	68	C34, T34
Fornieles et al.	2014	Community	Down Syndrome	Resistance Training	Salivary testosterone and immunoglobulin A	40	C16, T24
Ordonez et al.	2014	Community	Down Syndrome	Exercise	Inflammation	20	C9, T11
Rosety-Rodriguez et al.	2014	Community	Down Syndrome	Exercise	Inflammation	20	C9, T11
Seritan et al.	2014	Not clear	Fragile X	Memantine	Tremor	88	C45, T43
Melville et al.	2015	Community	Intellectual Disability	Walking	Physical Activity	102	C48, T54
Shields & Taylor	2015	Community	Down Syndrome	Physical Activity	Feasibility study	16	C8, T8
Boer, P. H. & Moss, S. J.	2016	Not clear	Down Syndrome	Physical Activity	Health and physical functioning	46	C16, T15, T15

Bouvet,C. & Coulet,A.	2016	Employment agency	Intellectual Disability	Relaxation	Self-esteem & emotional regulation	30	C15, T15
de la Torre et al.	2016	Community	Down Syndrome	Green tea extract	Cognitive training	87	C44, T43
Feldman et al.	2016	Community Living Associations	Intellectual Disability	Health Promotion program	Health Awareness	22	C10, T12
Kuppens et al.	2016	Not clear	Prader-Willi Syndrome	Growth Hormone	Body composition	27	C14, T13
Martins et al.	2016	Not clear	Down Syndrome	Dentistry – antimicrobial photodynamic therapy	Probing Pocket Depth	13	
Sano et al.	2016	Community	Down Syndrome	Vitamin E	Cognitive deterioration	337	C169, T168
Chan,J. S. L. & Chien,W. T.	2017	Institutions or community residential homes.	Intellectual Disability	Massage Therapy	Challenging Behaviours	42	C10, MT10, MSE11, MT-MSE11
Cooney et al.	2017	Institutions or community residential homes.	Intellectual Disability	Computer delivered Cognitive-Behavioural Therapy	Depression & anxiety	49	C25, T24
Harris et al.	2017	Multiple service providers	Intellectual Disabilities	Health Promotion program	Weight management	50	T26, T24
Jahoda et al.	2017	Multiple service providers	Intellectual Disabilities	Behavioural Activation	Depression	161	CT77, T84
Kim,S-S	2017	Employment & Welfare Agencies	Intellectual Disabilities	Endurance exercise & half-bath	Body composition & cardiorespiratory	24	C8, T8, T8

Kuppens et al.	2017	Not clear	Prader-Willi Syndrome	Growth Hormone	Metabolic Health	27	C14, T13
Ptomey et al.	2017	Community	Intellectual Disabilities	Health Promotion program	Weight management	150	CD72, T78
Silva et al.	2017	Occupational Centre	Down Syndrome	Wii-based exercise program	Physical fitness	27	C13, T14
Torres-Unda et al.	2017	Occupational Centre	Intellectual Disability	Movement-based Learning program	Functioning & Body Balance	32	C20, T21
Tyrer et al.	2017	Institutions or community residential homes.	Intellectual Disability	Nidotherapy	Challenging Behaviour	200	C115, T85
van Schijndel-Speet et al.	2017	Day Activity Centres	Intellectual Disabilities	Structured Physical Activity program	Physical activity	151	C70, T81

Notes: \*Open label, randomised, parallel group trial. \*\*Study ending early, \*\*\* UC = Usual Care group, ASK = the ASK diary group, CHAPS = the CHAPS health review group and CA = CHAPS and ASK group. \*\*\*\* APN = Advanced Practice Nurse intervention, HRA = Health Risk Assessment