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**Process evaluation in intellectual disability  
research: a case study and the need for  
adaptation of frameworks**

Elizabeth Randell<sup>1§</sup>; Rachel McNamara<sup>1</sup>, and Monica Busse<sup>1</sup>

Institutional Affiliations

1. Centre for Trials Research, Cardiff University, Neuadd

Meirionnydd, Heath Park, Cardiff, UK

[Randelle@cardiff.ac.uk](mailto:Randelle@cardiff.ac.uk)

[McNamara@cardiff.ac.uk](mailto:McNamara@cardiff.ac.uk)

[BusseME@cardiff.ac.uk](mailto:BusseME@cardiff.ac.uk)

§Corresponding Author

## **Abstract**

### **Background**

Involving adults with cognitive impairments, and specifically intellectual disability, in research is critical to developing appropriate and effective interventions but is highly challenging. Our aim was to examine where complexities lie in delivering research in underrepresented and hard to reach populations using an exemplar process evaluation conducted as part of a drug reduction trial.

### **Methods**

Quantitative methods were used to assess recruitment, adherence to the intervention and safety data. Qualitative interviews examined non-efficacy based barriers to drug reduction in clinical practice.

### **Results**

Feasibility of carrying out a drug reduction trial was limited by a lack of exploration of acceptability. Barriers to successful delivery included concerns around wider care team co-operation and consent procedures.

### **Conclusions**

It is important to consider interventions involving adults with cognitive impairment, and particularly intellectual disability, as complex. Current process evaluation frameworks require further adaptation to guide research and innovation in these populations.

**Keywords**

Intellectual Disability; Complex Intervention; Process Evaluation; Cognitive Impairment; Clinical Trial of an Investigational Medicinal Product

## **BACKGROUND**

The development and testing of interventions can be informed through use of research frameworks and process evaluation.

For example, the Medical Research Council (MRC) have produced guidance for the evaluation of non-pharmacological interventions they describe as complex (1) – interventions which are essentially ‘made up of various interconnecting parts’ (2). This has been supported by further guidance on conducting process evaluations to explain the way in which complex interventions work (3). While process evaluations can be stand alone pieces of work, they can also be embedded with clinical trials to answer questions around implementation, theory of change and how context impacts on the way in which the intervention was intended to work.

Research involving adults with cognitive impairments such as developmental, degenerative and psychiatric disorders (4) is critical to developing appropriate and effective interventions (e.g., such as those which aim to improve individuals’ quality of life (5)) and informing our understanding of underlying mechanisms. More specifically, clinical trials and other well designed studies that focus on the development and testing of interventions in these populations are however complex for a variety of reasons. They require co-operation of many

professionals, caregivers and 'gate-keepers' (6) primarily due to the nature of diminished cognitive functioning but also due to a variety of individual and contextual issues. Challenges around obtaining consent, providing appropriate study materials (6)(7) and ensuring adherence to study protocols are well known barriers (8). Given this complexity, such populations are often excluded from high quality research across disciplines (9) which in turn leads to a lack of evidence-based care. Absence of evidence can lead to inconsistent clinical practice that may not be cost-effective or even safe (10) highlighting a need for focussed research and in particular, trials of interventions for potential future use in clinical practice.

The aim of this paper is to examine where complexities lie in delivering research in underrepresented and hard to reach populations, specifically adults with intellectual disability.

Using the ANDREA-LD trial (ANTipsychotic Drug REDuction for Adults with Learning Disabilities) (11) as a case study we will explore what criteria are important in guiding researchers in this field as they make decisions about designing and evaluating interventions. Specifically we will focus on the inclusion of process outcomes and process evaluation for trials of Investigational Medicinal Products (IMP) in this population

and the timing of including such outcomes in the pathway of intervention development.

### **ANDREA-LD case study**

The ANDREA-LD trial was originally planned and implemented as a fully powered phase III trial of an IMP. The objective was to establish whether adults with intellectual disability who were routinely administered antipsychotic medication for the purpose of managing challenging behaviour could have that medication withdrawn without incidents of such behaviour increasing. The need for the research arose because although evidence supported the safety and efficacy of antipsychotic medication when used to treat individuals with severe mental illness, there was a lack of evidence for its use to treat challenging behaviour without this corresponding diagnosis. Further, individuals were not receiving regular review of this medication (11). The trial received ethical approval to open in April 2013 however, despite alterations to the study design it did not achieve its anticipated recruitment target and closed to recruitment in November 2015. The trial was set up to be delivered in primary care as this was where potential participants were most likely to present however, due to low uptake, recruitment was expanded to include secondary care.

Results were reported to the funder as an exploratory pilot study (11). During the trial it became apparent that a traditional linear pharmacological evaluation model did not wholly accommodate the complexities related to the context in which the trial was delivered. Trial objectives were not achieved in full due to reasons unforeseen at the outset and planning stages. Rather than a stand-alone pharmacological intervention, ANDREA-LD should by definition also have been considered as a complex intervention as the aim of reducing medication included a number of interacting components (e.g. prescribing and other therapies) with a number of parties involved (e.g. clinicians, families and carers and support staff) in different contexts (e.g. family homes, supported residences, primary care) and should ideally have included a specific evaluation of process alongside feasibility outcomes.

However, at the time the trial was designed, the MRC guidance was yet to be developed and process evaluations were not considered appropriate for clinical trials of investigational medicinal products (CTIMPs) thus no formal framework was used and only a relatively small component of the trial sought to explore what could be described as process evaluation elements and experiences of taking part through qualitative interviews with researchers, carers and participants. Here we will examine how the revised feasibility



outcomes needed to be considered alongside important process outcomes which could then be utilised to inform a more extensive process evaluation for use in fully powered trial.

### **ANDREA-LD methods**

The ANDREA-LD trial employed a mixed methods approach to capture and analyse data (Table 1). Quantitative methods were used to assess recruitment, adherence to the intervention and safety data. Qualitative interviews examined non-efficacy based barriers to drug reduction in clinical practice. The outcomes assessed were: i) how effective various recruitment routes were; ii) whether participants remained in the trial once recruited; iii) individuals' views on the acceptability of the trial design including their thoughts on the intervention and being part of the study; iv) how well participants were able to adhere to the intervention and (v) safety aspects of the trial.

#### *Recruitment and retention*

Quantitative recruitment outcomes were: (i) the number and proportion of General Practitioner (GP) practices or Community Learning Disability Teams that approached

patients and then proceeded to recruit them into the trial (ii) the number and proportion of participants who continued through the stages of the trial.

### *Acceptability*

Qualitative interviews with a sample of carers, clinicians who acted as Principal Investigators (PIs) and participants were undertaken to explore the challenges and experiences of taking part in the trial. The interviews examined motivations and concerns of taking part; how well individuals felt they were supported; how perceived reduction in medication might have led to attributions of behavioural changes; views on practical aspects of the trial such as taking medication, consent and data collection; general views on medication use for treatment of behavioural difficulties, and views on future medication use following the trial. Interviews with clinicians also asked about their use of the support package designed by clinical members of the trial team and how well they thought patients/carers managed taking part in the trial. Interview topics for participants focused on (a) reasons for taking part (b) how they felt they coped with taking part (c) their views on taking medication to help with behaviour.

### *Adherence to the intervention*

The intervention was designed so that medication (risperidone) was reduced for those in the reduction arm over four stages with the aim of full withdrawal within 6 months. Clinicians had the option of delaying any potential reduction in medication if they felt there was any concern. As this was a blinded trial using over encapsulated tablets, participants in the control arm followed through the same stages as those in the intervention arm but maintained their baseline levels of medication. Full adherence to the intervention was taken to mean a successful progression through each stage thus those in the reduction arm would achieve full withdrawal.

Participants entered into the study taking their usual prescribed dose of risperidone. The first stage of the intervention was designed to give participants time to get used to taking their medication in the form of over-encapsulated tablets (stage 0). The stages that followed were to reduce their medication levels (reduction arm only) by 25% at each time point (stages 1 to 4)(Figure 1). The levels of medication achieved at 6 months (so by stage 4) was maintained for a further 3 months with the blind still in place.

At 9 months, the blind was broken and all parties were informed of treatment allocation. Throughout the intervention, clinicians saw participants every month to

monitor their progression. If there was any concern about potentially reducing a participant's medication, clinicians had the opportunity to delay any changes in medication (i.e., to delay any of the 4 reduction stages). Therefore, it was possible for a participant to progress through all stages of the trial but not actually reach full reduction in medication. Information regarding decisions to continue through each stage was captured in real time by the study team.

#### *Adverse effects*

During the course of the trial, adverse effects were recorded in accordance with Clinical Trial Regulations (12). An adverse event consistent with the information set out in the Summary of Product Characteristics (SmPC) for risperidone was considered expected. Those events not expected, were recorded on the relevant case report form. All adverse events and pregnancies that occurred during the 12 months the participant was in the trial were reported.

## **Results**

### *Recruitment and retention*

Approaches were made to up to 500 potential sites to take part in the trial; 470 GP practices and 30 Community Learning Disability Teams (CLDT). Recruitment was originally intended to take place in primary care but only 59 of the GP practices approached expressed an interest, of which 16 became sites. From those 16 practices just 4 participants were randomised into the trial. While some degree of difficulty in recruiting participants was expected, the scale of problems experienced trying to recruit through primary care had not been anticipated and it took 12 months before permission was granted to extend recruitment to secondary care. This was in part due to conflicting views of the Trial Management Group, Trial Steering Committee and Funder as to whether this meant a fundamental change to the research question which was whether this type of medication reduction was possible in a primary care setting. Once resolved, a further 20 sites (Community Learning Disability Teams) were set up across south Wales and south west England. In terms of participants, 36 individuals were screened (five from primary care and 31 from CLDT) with 22 going on to be randomised. Follow-up data at six and nine-months post-randomisation was obtained for 17 participants; ten intervention and seven control participants (77.3% of those randomised).

### *Acceptability*

Interviews were held with individuals in both arms of the trial – 16 carers (11 professional carers and five parents) and four participants. Because the focus of recruitment was in secondary care, only CLDT clinicians were invited to interview with 11 agreeing. Data were analysed using an abductive approach to thematic analysis with the researcher blind to treatment allocation.

#### i. Reasons for participating

Clinicians, carers and participants agreed that this was an important research area. For clinicians, it was thought involvement could be of benefit to the wider CLDT team in raising awareness of anti-psychotic prescribing and research.

*Clinician 6: "I wanted to support high quality research, firm believer that we need applied research, and jobbing psychiatrists being part of research..."*

Carers and participants' motivations were mainly positive and focussed on wanting to reduce medication where possible to minimise it's impact on participants' personality. One

participant was keen to see if she could 'change her life' by controlling her mood swings.

ii. Views about the trial

Given that for many of the carers and clinicians, this was the first randomised controlled trial they had been part of, concerns about the trial were relatively few. There was some apprehension about not knowing treatment allocation but an understanding that this was necessary to deliver results.

*Carer 9 (Staff): "So yes I feel that the project was very well managed and very supportive."*

iii. Potential attributions of behavioural changes

Reports of negative behaviours arose from carers during the trial: however it was not always possible to attribute these to medication reduction given that some reports came from those in the control group. In addition, many behaviours described as challenging were present before the participant entered the trial.

There was consensus among clinicians that participant behaviour was generally stable and in cases where this was not the case, there were often other explanations such as

infection, hospital visits or changes to other therapies. Both clinicians and carers reported some positive changes in behaviour as well, including 'regaining' personality traits, or becoming more themselves.

*Clinician 4: "I did rely a lot on carers or family members to tell me about the behaviour. I always told the carers and the person "please do let me know if you see any significant changes, anything that will concern" I made a point every single time, um but sometimes with the carers whether they could read more into something or not, because there was one person who unfortunately pulled out, they, they pulled out because they saw a change of behaviour and the person was still on their, I think it was still on their first month, therefore he wasn't yet on the active medication study, he was still just on the same dose..."*

#### iv. Practical aspects of the trial

Key areas of concern included: consent procedures (particularly the role of personal legal representative), whether individuals with autism should be included (i.e., inclusion criteria) and the delivery of the trial medication as an encapsulated tablet.



*Clinician 3: “ We did spend quite a lot of time trying to find out who was the proper person to discuss informed consent and talk about informed consent, you know in the paperwork it was very clear that the carers could give full consent, but the reality was that the carers were not happy, were quite uneasy with that.”*

*Clinician 7: “I think the population we looked at was correct, I think the only difficulty that I saw was, we do have patients with autism and sometimes they’re on small doses of antipsychotics and trying to, although it’s not for a psychosis, it’s for other reasons, so I think they may have been included. And when they’re taken off, even a small dose of antipsychotics they had difficulties I think, so that maybe something, that they’re a slightly separate population to people without autism.”*

Despite these concerns, none of the stakeholders voiced the opinion that a trial such as this was not possible, even with participants in residential homes.

#### *Adherence to the intervention*

Full adherence and progression through all four stages of intervention/control was achieved by 13 of the 22 participants randomised (59.1%; seven intervention, six control). The full

breakdown is detailed in Table 2 which shows not only those who successfully progressed through each potential reduction stage but also those who were delayed due to concerns. Stage 0 (run-in stage to get used to new presentation of medication) to stage 1 (first reduction stage) = 86.4% (n=19); stage 1 to stage 2 = 59.1% (n=13); stage 2 through to stage 4 = 59.1% (n=13).

#### *Adverse effects*

Four Adverse Events (AE) and one Serious Adverse Event (SAE) were reported. The SAE was categorised as ‘an event which required intervention to prevent outcomes such as hospitalisation’ after a reported deterioration in the participant’s mental health. The outcome of the clinical review was that these symptoms were not a side effect of the trial medication but a recurrence of symptoms masked by the antipsychotic medication.

Important insights into process can be gained from the feasibility outcomes of the ANDREA-LD trial. In future, more extensive process evaluation findings could inform the design of a fully powered effectiveness trial for adults with intellectual disability including its own process evaluation to

inform interpretation of results. In the planning stages of ANDREA-LD, prevalence figures supported the idea that the majority of potential participants would be seen in primary care and therefore that was the best place to focus recruitment. What hadn't been fully appreciated was the scale of GPs concerns about recruiting through primary care and interviews with those who did not recruit would have been beneficial to understand these concerns more fully. There was also considerable variation in readiness of intellectual disability services to support those wishing to take part in the reduction of antipsychotic medication. One of the key challenges was around others concerns that reduction in medication was causing negative behaviour change rather than whether or not the medication *could* be reduced. The trial demonstrated that incidents where it was necessary to remove the blind (i.e. where there were reported incidences of challenging behaviour and/or decline in mental health) were equal between groups implying this was a concern independent of intervention. Attribution of cause was given to the potential for medication to have been altered rather than to an actual change. As such, the complexities of the settings in which the intervention (the drug reduction) took place seemed to have the greatest impact on delivery of the trial.

## **Discussion**

Reviewing the ANDREA-LD trial it seems clear that the intervention had many more interacting components than simply a drug reduction programme. We reflect on the complexity drugs trials involving adults with cognitive impairment, in particular intellectual disability, and how and when process evaluations in this type of research might be introduced to aide the planning and design of future research and the importance of considering the wider context of trials in this population.

In ANDREA-LD, it was apparent that much of the concern from clinicians around the intervention did not relate to the practicalities of clinical management (participants could safely progress through to full withdrawal) but rather to wider care team co-operation (as also reported by Deb et al. (13)) and some elements of research procedure - specifically consent. Clinicians and carers would have been familiar with the Mental Capacity Act (14) which makes provisions relating to the care, treatment and decisions made on behalf of people who lack capacity. However in drugs trial, other regulations (12) take precedence over this elements of this Act. As the qualitative results revealed, there was uncertainty around the regulations

and in particular carers' were not confident in taking on the role of personal legal representative.

Use of blinded medication in the trial sought to remove bias reported in open label trials in similar populations (15)(16) as findings from these studies suggested that staff and carer reports of worsening behaviour might have been influenced by their expectation following antipsychotic reduction. However this was also shown in ANDREA-LD. Preliminary qualitative work could have been conducted with Patient and Public Involvement (PPI) groups and clinicians with a focus on concerns around process and their expectations of a drug reduction regime prior to an effectiveness evaluation.

The feasibility outcomes gave insights into elements of process in the ANDREA-LD trial. It is apparent that insufficient understanding, insight and consideration was given to the complex setting and systems in which the intervention was being delivered. Recruitment into the trial and support to achieve the delivery of the drug regime was dependent on the co-operation of various parties including the participant and gatekeepers such as carers, clinicians and clinical teams.

### ***Rethinking complex interventions***

Clinical research involving interventions of Investigational Medicinal Products (IMP) commonly develops in a phased

approach. Typically, this will involve early testing for safety in a few human participants through to larger scale evaluations to determine if the treatment is effective. In this way, clinical trials of IMPs tend to take place in a linear fashion, focusing purely on the mechanisms, pharmacokinetics, dynamics, safety and efficacy of the medication under investigation. Given this, identification of key contextual information about the environment in which the intervention is being implemented may be missed. This can be particularly true when thinking about research involving adults with intellectual disability or cognitive impairment. For example, the environments or settings in which they live might be complex with many interacting components. Individuals may live with full- or part-time caregivers; they may live in a family home or in support accommodation; they may have one-to-one support or be cared for by a wider team. Researchers conducting trials of IMPs in this population therefore are not routinely examining how implementation of the intervention might be different depending on setting, why it works and whether it works in the same way for everyone. Reports of trial findings are therefore potentially missing vital contextual information which could describe key elements essential for success or failure of implementation.

In contrast, the MRC guidance (17) describes the process of complex intervention development in a similar phased approach to drug models but emphasises that it may not necessarily follow a linear sequence. The authors of the guidance also acknowledge the role of context and the importance of demonstrating strong theoretical underpinnings to interventions and the use of logic models to conceptualise and analyse complex interactions. The guidance also includes the importance of early phase piloting work and local tailoring of interventions (1) however complexity was still thought to lie within the components of the intervention. The impact of context was also challenged by researchers as the guidance assumed this to be static rather than having '*dynamic influence*' (18) especially on intervention development (19). Hawe suggests a complex systems approach to complex interventions where context is in fact the central component of intervention complexity. This in turn has implications for the way in which interventions are evaluated and refined. The MRC have since reviewed their 2008 guidance (20) and will be shortly publishing new guidance which incorporates the importance of taking a systems perspective. The relevance of this for trials involving adults with intellectual disability and cognitive impairment is likely to be important given the complexity of the systems within which they live.

The key learning from the ANDREA-LD trial is that interventions for adults with intellectual disability are complex with context being a key component of that complexity and the importance of gaining insight into process outcomes throughout intervention development. While there are frameworks available to support and guide intervention design of CTIMPs, consideration needs to be given to whether they go far enough in covering the complexities of research in this population and whether creation of a specific process evaluation framework would then feed into further implementation methodology to influence change in practice. Identifying important reporting criteria of key components of an intervention in such a populations may prove helpful to researchers deciding on future research design.

We recommend further work to establish whether the process evaluation model could be further adapted or expanded to guide research and innovation in populations of adults with intellectual disability and cognitive impairment more generally and when process outcomes should be included in both feasibility trials and fully powered effectiveness trials. In doing this, researchers would be working towards creating a more unified evidence based approach to their work.



## References

1. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions : new guidance. BMJ. 2008;
2. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. British Medical Journal. 2000.
3. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015;
4. Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders. Vol. 4, The Lancet Psychiatry. Elsevier Ltd; 2017. p. 339–46.
5. Ramerman L, Hoekstra PJ, de Kuijper G. Health-related quality of life in people with intellectual disability who use long-term antipsychotic drugs for challenging behaviour. Res Dev Disabil. 2018;75.
6. Shepherd V, Wood F, Griffith R, Sheehan M, Hood K. Protection by exclusion? the (lack of) inclusion of adults who lack capacity to consent to research in clinical trials in the UK. Trials. 2019.

7. Shepherd V, Wood F, Griffith R, Sheehan M, Hood K.  
Research involving adults lacking capacity to consent: A content analysis of participant information sheets for consultees and legal representatives in England and Wales. *Trials*. 2019;
8. Spong CY, Bianchi DW. Improving Public Health Requires Inclusion of Underrepresented Populations in Research. Vol. 319, *JAMA - Journal of the American Medical Association*. 2018.
9. Prusaczyk B, Cherney SM, Carpenter CR, DuBois JM.  
Informed Consent to Research with Cognitively Impaired Adults: Transdisciplinary Challenges and Opportunities. *Clin Gerontol*. 2017;
10. Greenhalgh T, Howick J, Maskrey N, Brasseley J, Burch D, Burton M, et al. Evidence based medicine: A movement in crisis? *BMJ (Online)*. 2014.
11. McNamara R, Randell E, Gillespie D, Wood F, Felce D, Romeo R, et al. A pilot randomised controlled trial of community-led antipsychotic drug reduction for adults with learning disabilities. *Health Technol Assess (Rockv)*. 2017;21(47).
12. UK Statutory Instruments. The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.

Statut Instruments. 2006;2006(1928).

13. Deb S, Nancarrow T, Limbu B, Sheehan R, Wilcock M, Branford D, et al. UK psychiatrists' experience of withdrawal of antipsychotics prescribed for challenging behaviours in adults with intellectual disabilities and/or autism. *BJPsych Open*. 2020;6(5).
14. Shickle D. The Mental Capacity Act 2005. *Clin Med J R Coll Physicians London*. 2006;6(2).
15. Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, et al. Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: A randomised controlled trial (NACHBID). *Health Technol Assess (Rockv)*. 2009;13(21).
16. De Kuijper G, Evenhuis H, Minderaa RB, Hoekstra PJ. Effects of controlled discontinuation of long-term used antipsychotics for behavioural symptoms in individuals with intellectual disability. *J Intellect Disabil Res*. 2014 Jan;58(1):71–83.
17. Mrc. A FRAMEWORK FOR DEVELOPMENT AND RCTs FOR COMPLEX INTERVENTIONS TO. *London Med Res Counc*. 2000;(April).
18. Wilson PM, Boaden R, Harvey G. Plans to accelerate innovation in health systems are less than IDEAL. *BMJ*

Quality and Safety. 2016.

19. Hawe P, Shiell A, Riley T. Theorising interventions as events in systems. In: American Journal of Community Psychology. 2009.
20. Craig P, Matthews L, Moore L, Simpson S, Skivington K. Developing and Evaluating Complex Interventions. Draft of updated guidance. 2018.

**Table 1.** Summary of process evaluation components and data source

<b>Process Evaluation Component</b>	<b>Key questions</b>	<b>Analysis</b>	<b>Data Source</b>
Recruitment	Where were participants recruited from?  Could participants be recruited from both primary and secondary care?	Number and proportion of General Practitioner (GP) practices or Community Learning Disability Teams that progressed from initial approach to recruitment of participants	Screening log
Retention	At what point in the intervention was drop-out experienced?	Number and proportion of recruited participants who progressed through the various stages of the study.	Withdrawal form
Acceptability	How acceptable was the trial to all involved?	Qualitative interviews with a proportion of carers, Principal Investigators (PIs) and participants	Transcripts of recorded interviews
Adherence	Did participants adhere to the intervention as it was planned	Study medication delivery and progression through study phases was reported	Session records with trial clinicians
Adverse Effects	Were there any adverse effects of the intervention	Numbers of adverse effects were reported and monitored	Serious Adverse Event form

**Table 2.** Participant adherence to the stages of the intervention

	Stage		Control	Intervention	Overall
Total randomised			11 (100.0)	11 (100.0)	22 (100.0)
Intervention receipt	Stage 0 to Stage 1	Withdrew before progressing to Stage 1	2 (18.1)	1 (9.1)	3 (13.6)
		Progressed from Stage 0 to Stage 1	9 (81.8)	10 (90.9)	19 (86.4)
	Stage 1 to Stage 2	Withdrew between Stage 1 and Stage 2	3 (27.3)	1 (9.1)	4 (36.4)
		Delayed progression between Stage 1 and Stage 2	0 (0.0)	2 (18.1)	2 (9.1)
		Progressed from Stage 1 to Stage 2	6 (54.5)	7 (63.6)	13 (59.1)
	Stage 2 to Stage 3	Withdrew between Stage 2 and Stage 3	0 (0.0)	1 (9.1)	1 (4.5)
		Delayed progression between Stage 2 and Stage 3	0 (0.0)	1 (9.1)	1 (4.5)
		Progressed from Stage 2 to Stage 3	6 (54.5)	7 (63.6)	13 (59.1)
	Stage 3 to Stage 4	Withdrew between Stage 3 and Stage 4	0 (0.0)	1 (9.1)	1 (4.5)
		Progressed from Stage 3 to Stage 4	6 (54.5)	7 (63.6)	13 (59.1)
	Stage 4 to Stage 4 (repeat 1)	Withdrew between Stage 4 and Stage 4 (repeat 1)	0 (0.0)	1 (9.1)	1 (4.5)
		Progressed from Stage 4 to Stage 4 (repeat 1)	6 (54.5)	6 (54.5)	12 (54.5)
	Stage 4 to Stage 4 (repeat 2)	Progressed from Stage 4 to Stage 4 (repeat 2)	6 (54.5)	6 (54.5)	12 (54.5)
	Stage 4 to Stage 4 (repeat 3)	Progressed from Stage 4 to Stage 4 (repeat 3)	6 (54.5)	6 (54.5)	12 (54.5)
	Participant follow-up	Completed six-month follow-up		7 (63.6)	10 (90.9)
Completed nine-month follow-up		7 (63.6)	10 (90.9)	17 (77.3)	



**Figure 1.** Participant flow diagram through the ANDREA-LD trial