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Trials and Tribulations in Early Autism Intervention Research (in press, *JAACAP*, 01/03/2019)

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Despite a slow start[1], the past 15 years has seen an unprecedented increase in the number and quality of randomised controlled trials (RCTs) being conducted in the early autism field. This is welcome because many young children with autism struggle to communicate and interact with others; restricting their opportunities to learn and develop and impacting on their parents who can find their child's behaviour perplexing and challenging to manage. However, as with so many areas of clinical science, with progress come challenges. The authors[2] report on a multi-site RCT of the Early Start Denver Model (ESDM) an intensive, naturalistic developmental-behavioural intervention programme. The original small-scale (n = 48) ESDM study[3] found improvements in IQ and adaptive behaviour (largely in the language/communication domains) and a marginal

improvement in diagnostic classification but no differences on continuous measures of autism severity. The study is highly cited and has been influential as a key part of the evidence for proponents arguing for the effectiveness of comprehensive early intervention programmes.

The current study has a number of strengths, including a larger sample size (n = 118), young age of children at enrolment (14 to 24 months), multiple sites including sites naïve to implementing the intervention, and the use of an intention-to-treat analysis. Intervention included 3 months of parent coaching in the ESDM model, followed by 24 months of 1:1 therapist implemented ESDM delivered in home or day care settings for ~14 hours per week with ongoing parent coaching, and fidelity of implementation was high. The findings are a partial replication of the original study, but the discrepancies are significant and may require the field to take stock of how secure the evidence for effectiveness of the ESDM approach is, as well as to learn the lessons we can from the difficult science of clinical trials. The study found a significant group-by-time effect for changes in language ability in favour of the ESDM group compared to community controls who received 'treatment as usual' (TAU) but this was qualified by a group-by-time-by-site interaction: in two of the three sites the ESDM group had significantly superior language change compared to the TAU group but in the third site the TAU group had a superior (but nonsignificant) increase. In contrast to the original study there were no group differences in overall IQ or adaptive behaviour but consistent with the original study the groups did not differ on a continuous measure of autism severity (Autism Diagnostic Observation Schedule (ADOS[3])). A pre-planned moderation analysis did not find effects for baseline IQ, language, autism severity, measures of play or joint attention ability or maternal education on language outcomes.

Reproducibility of findings across multiple trials should be the minimum standard for assessing efficacy of any treatment[4]. The replication of improved language outcomes following ESDM intervention in the present study and the previous pilot trial is then perhaps then the most secure clinical 'take home' message. It is also an important one due to the negative impacts of the limited language and communication abilities present in many young children with autism, as

outlined above. However, other findings were not replicated in this larger multi-site study and many in the field will want to understand why this might be. Neither global IQ, nor adaptive functioning improved more in the ESDM group than in the TAU group. The authors discuss several possibilities, including the availability of intensive interventions for those not randomised to the 'active' treatment (the TAU group received a mean of ~14 hours per week of 'community intervention'), that may include interventions adopting similar or overlapping approaches. One limitation of comparing an active treatment group, where one measures the fidelity of implementation of the treatment model, to TAU which families will access in a number of ways from different providers is that one does not know and cannot measure what and how well 'treatment as usual' has been implemented. Randomised trials test how the two groups compare to each other across the course of the study, from baseline to endpoint. Any between-group differences are likely to be due to the treatment itself because random allocation will distribute differences in other factors that may affect child outcome (whether or not one has characterised these at baseline) equally across both arms. Trials do not allow one to make a judgement about the effectiveness or overwise of the unmonitored and uncontrolled TAU on child outcomes.

This raises the issue of how best to test the efficacy of a time- and cost-intensive treatment (such as ESDM) against an alternative treatment unless the alternative also provides likely benefit. This relates to the critical principle of 'equipoise' that one can only conduct RCTs if the ultimate effectiveness of a particular treatment is unknown, since otherwise it would be unethical to randomise participants to the non-target intervention arm of a trial. Other treatment designs can also be informative, for example equivalence trials where participants are randomised to two competing active treatments and the fidelity of implementation of both interventions are controlled and monitored by the trial team.

Consistent with the previous small-scale study[3] groups did not differ at outcome in autism severity, as measured by the ADOS. Few interventions when tested in RCTs have shown reductions in symptom severity in early autism trials (see[6], for a rare exception). This raises several

questions, ranging from the appropriateness of the ADOS measure – designed as a diagnostic assessment – as a continuous measure of autism severity in clinical trials[7], to what the limits of even an intensive, comprehensive programme such as ESDM may be to effect change in young children with autism (at least in the short term). There is currently much debate in the autism field about what the goal of early interventions should be, how to measure 'outcomes', and who decides what treatment targets and outcomes should be[8].

Developing a mature science of clinical trials in the early autism field will take time and for historical reasons[1] the start of this process was delayed. Some may see the findings of the present study[2] as a set-back or disappointment given the initial positive findings of the pilot trial[3]. However, a more constructive response would be to take what lessons we can from this ambitious and well conducted study and to learn from them. First, there is consistent evidence from both studies that the ESDM intervention can improve language outcomes for at least some children with autism. This finding is also supported by a range of other developmental-behavioural early intervention trials[9]. Second, we need to think smarter about trial design and how to test the relative benefits of different interventions with different mechanism and outcome targets. Other critical design factors such as comparing length and intensity of treatment or the use of equivalence or sequential trial designs have barely begun in the autism field (see[10], for a rare exception). One can look across to the general child psychological therapies field and see what a more mature clinical trial literature may look like one day in the future; for example, Weisz and colleagues[11] meta-analysed a pool of 447 studies comprising over 30,000 youth conducted over 50 years. Finally, we need to begin a second-generation of early autism intervention trials where there is more collaboration between groups conducting trials; so that essential components of a mature trial science can emerge. These include groups testing interventions independently from intervention originators, comparing different interventions with each other, and ensuring that trial protocols include common elements – particularly outcome measures – so that systematic reviews and meta-analyses can be conducted in the future. Bring on the trials; learn from the tribulations!

[word count = 1,259]

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