Using intervention trials in developmental psychiatry to illuminate basic science
Jonathan Green and Graham Dunn

Summary
We discuss the nature of intervention in developmental psychiatry and the implication of this for clinical trials. New ideas in the design of randomised trials for complex interventions, along with recent statistical advances in causal analysis, give such trials additional potential as a means by which to study the basic science of complex developmental disorders. The challenge for designers of trials is to model designs effectively to make best use of these new opportunities. We give examples of how this might be done and discuss implications for future trials designs in the area.

Declaration of interest
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Trials and developmental research
Substantial trial funding is a major research investment and should maximise its scientific output. The first priority is naturally to test the effectiveness of interventions but, when appropriately designed, we argue that trials in developmental psychiatry can and should also be used to illuminate basic science. Whereas academic and funding traditions can sometimes act to pull apart basic science and intervention research, this use of trials potentially provides a more integrated clinical research approach giving added value to expensive trials.

Developmental intervention
The classic view of treatment – as an episode of care of discrete disorder leading to reversal or removal of pathology – rarely applies in developmental disorder. Treatments here are rarely definitive or short term. They often need phasing over a much longer period and aim to target the developmental course of a disorder to alter its primary progression (insofar as this is tractable), or its secondary sequelae. Research into the multiple varying influences on the course of disorders has led to the tendency for such interventions to become more complex and multimodal. Such intervention can be conceptualised as a kind of ‘developmental perturbation’ in longitudinal course of a complex disorder.

New trial designs
Testing such interventions raises significant challenges to trial design, but also opportunities. For instance, so-called ‘hybrid’ clinical trial designs judiciously add elements from longitudinal association studies to the classic randomised controlled trial. Experimental studies generate methods and hypotheses regarding proximal mediators or moderators of treatment effect; the longitudinal design adds repeated measures analysis of proposed risk and protective factors – so that the two arms of the trial become in effect parallel longitudinal cohort studies. In principle, such hybrid trials can be used to study questions as diverse as causal effects in complex disorders, gene–environment interactions and the timing of the effect of risk or protective factors in development.

The idea of combining the best elements of randomised intervention trials with the use of statistical and econometric methods characteristic of observation studies has also been advocated in the social sciences. Bloom argues that by combining the two approaches investigators ‘can capitalise on the strengths of each approach to mitigate the weaknesses of the other’. He builds on ideas first proposed by Boruch to advocate methods to evaluate the effects of treatment received from the results of randomised trials in which not everyone receives the treatment they are offered.

Causal inference in analysis
Since the late 1980s there have been exciting developments in both statistics (particularly medical statistics) and econometrics for the use of so-called ‘causal inference’ in the modelling of the influences of post-randomisation covariates (levels of treatment adherence, surrogate endpoints and other potential mediators) on final outcome. In considering the possible causal influence of an intervention on outcome from data in an observational study there is always the possibility of an unmeasured variable (U1, say – Figs 1 and 2) which is associated with receipt of the intervention and also has a causal effect on the outcome. The variable U1 is known as a hidden or unmeasured confounder in the epidemiological literature and as a hidden selection effect in econometrics. In the presence of U1, straightforward methods of estimating the effects of intervention on outcome (through some form of regression model, for instance) will lead to biased results. When there is a potential mediator involved the situation is considerably more complex. Here there might be hidden confounding between intervention and mediator (U2) and also between mediator and outcome (U3). The great strength of randomisation is that it breaks the link between intervention and outcome (giving the possibility of valid intention-to-treat estimates) and between intervention and mediator. Hence, both U1 and U2 are no longer a problem. The effects of U3 (what Howe et al call mediated confounding), however, remain. It is the possible (or, in fact, very likely) existence of U3 that is the major challenge to valid inference from trials (including inferences regarding developmental causality). Typically it is implicitly assumed to be absent and the vast majority of the investigators
using methods such as those first introduced by Baron & Kenny®,
seem to be blissfully unaware of this threat to the validity of their
results.

The key to the solution to this validity threat comes from
recent statistical developments that enable us to evaluate both
direct and indirect (mediated) effects of a randomised inter-
vention on outcome in the presence of mediated confounding.
The solution involves finding baseline variables (called instrumen-
tal variables or instruments) which have a strong influence on the
mediator (and hence on the outcome) but a priori can be assumed
to only influence outcome via the mediator (i.e. complete
mediation). Further technical details can be found elsewhere.5,6

Linking methodological developments
with clinical questions

The challenge for designers of clinical trials here is to identify real-
world clinical analogues of these instrumental variables within a
trial design, which can then be used simultaneously to test relevant
aspects of treatment process and of developmental theory. For
instance, in developmental psychiatry, parent-mediated treat-
ments of child disorder are common. The final aim of such inter-
ventions is to improve child functioning; but the immediate focus
is on working with the parent to improve parent–child interaction.
It is this parent–child interaction (an aspect of the non-shared
environment for the child) that will be the hypothesised mediator
of change in the primary target child outcome (say behaviour
disorder). However, this interaction is also likely to be influenced
by pre-treatment parental variables such as personality or social
functioning. Such parental variables may have a direct effect on
child outcome through shared genetic effects in some disorders,
but in the majority of cases will have an impact on the result of
treatment (child functioning) largely or solely through their effect
on the parent–child interaction. The mediation effect of the
parent–child interaction is then said to be moderated by the pre-
treatment parental trait. Measurement of this parental variable
can therefore have two simultaneous and related uses: first, as a
real-world factor in the child outcome of treatment; and second,
fulfilling statistical conditions to be used as an instrumental
variable as described above in the context of U3. Including such
variables allows the trial analysis to define more precisely the
causal roots of a treatment effect: the instrumental variable (in this
case parental functioning) is not just used as a covariate against

which to undertake the rest of the analysis but is entered into a
more complex causal analysis modelling. Although few trials of
parent-mediated treatments report additional measurement of
relevant parental variables, even though they are theoretically
relevant to causal effects, a recent trial that did measure them®
found that they contributed to the explanation of treatment
variance. Developmental psychopathology research has been
challenged by difficulties in untangling the causal relationships
between parental functioning, parent–child interaction and child
functioning. Such designs could help address these causal
questions in a powerful and novel way.

A second area in which this approach has been applied pro-
ductively is in the investigation of the effect of process variables
such as therapeutic alliance.10 A worked example of the analysis
of therapeutic alliance in trial in this way is set out in Dunn &
Bentall.6

Implications for clinical trials

Key criteria for the kind of trial in which developmental questions
can be tested were identified by Howe et al:3
(a) the intervention must be theory-based and clearly constructed;
(b) the proximal target of the intervention should be a variable
known from developmental theory to be a likely candidate
for an important developmental process worth testing; this
implies that the developmental theory behind a particular
research question must be mature.
(c) the intervention must have been shown in pilot studies to be
able to change this intermediate mediating variable as well as
the outcome;
(d) sampling for the trial needs to be consistent with the theories
to be tested in the developmental aspect of the trial.

It is self-evident that funding for such a design must be
adequate and that there needs to be active collaboration between
designers of clinical trials, statisticians, and developmental
scientists in the design phase.

Concluding remarks

There is potential synergy between methodological developments
in causal analysis, the need to have trials better modelling the
process and outcome of complex interventions,7 and basic science
Research in developmental psychiatry. Clinical decision-making as well as scientific studies rely on implicit procedures for establishing causal relationships. New causal analytic methods in trials may lead to better understanding of how interventions have their effect, while simultaneously allowing testing of basic science hypotheses. These considerations could inform future studies of developmental interventions and suggest that funding for clinical trials should not necessarily be considered separately from basic science research.

Jonathan Green, Division of Psychiatry, University of Manchester; Graham Dunn, Health Methodology Research Group, University of Manchester, UK

Correspondence: Jonathan Green, Room 4.319, 4th Floor (East), University Place, University of Manchester, Oxford Road, Manchester M13 9PL, UK. Email: jonathan.green@manchester.ac.uk

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