MRC Autism Research Forum

Interventions in Autism

Date: 10 July 2003
Location: Commonwealth Institute, London

Aim: The aim of the forum was to bring academics in relevant disciplines together, to discuss the study of interventions in autism spectrum disorder research. The expectation was that these broad discussions would aid interested researchers to submit high quality proposals for research in areas that had been highlighted in the recent MRC Review of Autism: Causes and Epidemiology, but also to provide evidence based interventions.

Professor Carol Dezateux (Professor of Paediatric Epidemiology at the Institute of Child Health, and Chair of the MRC Autism Research Steering Group) began the meeting by briefly described the MRC Autism Research Initiative. This initiative was set up by the MRC in the light of the £2.5 million given by the English Department of Health, and the subsequent £250,000 from the Chief Scientist’s Office of the Scottish Executive, to take forward the research recommendations of the MRC Review on Autism: Epidemiology and Causes (2001), but to also include research on interventions.

Dr Sandy Oliver (Institute of Education, London) gave a presentation on some issues surrounding patient-centred outcomes. Patient, carer and family involvement can be valuable because intervention research can be subjective in nature (for example the choice of outcomes, interventions for comparison, how effects are measured), and so research designs can be enhanced through their involvement. Patients, families and carers can contribute substantially to the choice of research questions, how the research is to be conducted, and how the findings could be interpreted and used. Methods for patient and family involvement are being developed by collective experience, a growing literature, and patients and families themselves. These individuals can make an important contribution in helping the researchers ensure that relevant outcomes are considered, be they a reduction in symptom severity, improved patient satisfaction or quality of life. Patients and families could be involved in eliciting ideas or coming to a decision, through consultations or collaborations, in a variety of ways. Dr Oliver concluded by reiterating the importance of identifying patients’ perspectives and the need to continue to develop and implement novel methods of involvement.

Professor Diana Elbourne (Institute of Education/ LSHTM) gave an overview of the evaluation of interventions. Randomised controlled trials (RCTs) were acknowledged to be the “gold standard” methodology for the evaluation of interventions, with the caveat that RCTs were not feasible for every intervention. Key steps in the evaluation of any intervention should be: to formulate a testable hypothesis; to define clearly the intervention(s), outcome(s), reference and study populations; to
calculate the appropriate sample size; to allocate participants to interventions; to collect outcome data; and then to analyse and report the results.

The formulation of the hypothesis to be tested was agreed to be essential, being usually based on scientific plausibility, probably informed by earlier, non-randomised, studies, animal and in vitro experiments, and in the context of systematic reviews or meta-analyses. Interventions could be preventive or therapeutic measures, as well as more complex interventions or packages of care. Outcomes should be meaningful, clearly defined, and measurable. The study population, which should be explicitly defined in terms of inclusion/exclusion criteria, generally aims to be representative of reference population, to which results of any trial would be extrapolated. The sample size should be sufficient to be confident that a real effect would not missed, if one existed, and that a small effect was not over-estimated.

Observational studies can be used to make comparisons between interventions, but may give misleading results about effects of such interventions because of selection biases at entry to the comparison. A random allocation of interventions in RCTs was the most scientifically rigorous way of comparing groups as it ensured differences between these groups were due to chance, but this approach would only reduce selection biases at trial entry if the allocation was concealed in some way. The importance of reducing other biases was emphasised. Such biases include selection biases after trial entry, concomitant treatment bias, and assessment bias.

Suitable analysis and reporting was a key part of the evaluation of an intervention, with the importance of pre-specifying analyses being emphasised. The importance of satisfactory reporting the outcome of any study was emphasised, as non-publication could lead to potential publication bias when all the available evidence was assessed. The recent, more widespread use of the CONSORT statements had been a significant development in the quality of the reporting of clinical trials.

Once a trial had been undertaken and subsequently reported, it was important that the data obtained should be considered alongside other trials, preferably through meta-analyses or systematic reviews, such as those undertaken by the Cochrane collaboration. A meta-analysis of the results of several similar trials could produce an overall estimate of effect size with tighter confidence intervals, and allow the investigation of heterogeneity. It was agreed that it was important to ensure that clinical trials were conducted within an ethical framework, and the specific issues that arose when participants were children or adults not able to understand sufficiently to give informed consent.

There was a short presentation by Professors Geraldine MacDonald (School for Policy Studies, Bristol University) and Stuart Logan (Penninsula Medical School) on existing systematic reviews on the effectiveness of interventions in ASDs. There were only two completed Cochrane reviews and two other reviews in Database of Abstracts of Reviews of Effects (DARE), with 5 further Cochrane protocols, where systematic reviews were either planned or underway. A database search had revealed 176 studies, considering 92 different interventions, with a large number of different outcomes being assessed.
It was evident that there were a relatively large number of trials for interventions in ASDs, although a large proportion had dealt with pharmacological treatments. Few trials had tested current mainstream interventions, and the quality of trials was variable, with a wide variety of outcome measures, a lack of clarity, and inconsistency of study population. The dearth of studies in adults was highlighted. For the future, it was recommended that systematic reviews summarised data (including less rigorous evidence) on promising educational and psychological interventions, and then trials of promising interventions could be undertaken, in a multi-centre design, with appropriate outcomes and prioritised by a cost-benefit analysis.

A number of issues were discussed in an informal, open manner:

**Outcomes for intervention in autism spectrum disorders (ASD)**

When considering specific outcomes to evaluate interventions in people with ASDs, it was acknowledged that at present there was no generally accepted measure. There was a need for the development of specific outcomes which should be related to the core deficits in autism spectrum disorders, relevant to the aims of the intervention, and should be patient-centred. It was not clear that a decrease in core deficits necessarily equated to an increase in quality of life. The importance of understanding why some individuals didn’t respond to a potential intervention, whereas others did, was agreed to be a key issue.

One issue highlighted was the degree of severity of the impairments may vary with time for most people with ASDs, and individuals may develop compensatory mechanisms. Ideally a good outcome measure would be able to look at along a spectrum of severity. The potential danger of comparison with inappropriate development stages when developing interventions or outcomes was highlighted.

There was discussion around the concept that a primary outcome measure may not demonstrate any change, but the overall quality of life may have altered; the use of a surrogate primary outcome measure may alleviate this potential problem. Other measurement issues discussed included the need to measure across the ability span, the potential to assess possible effects on parents or carers of an intervention for a person with ASD, and the use of diagnostic measures as outcome measures (e.g. ADOS subset of items).

One possible way forward that was suggested was to consider multiple outcomes, and regard ASDs as a multivariate disorder, rather than a univariate disorder along a spectrum of severity.

**Across the Age and Severity Spectrum**

Participants acknowledged that there was a lack of understanding about the natural history and progression in ASDs, and that understanding patterns of development and change may help in the development of a sensitive, discriminatory measure.
Furthermore an intervention developed for young children may well be inappropriate for adults.

When considering the evaluation of interventions for very young children, it was agreed essential to have parents fully engaged and participative in any study.

Co-morbidity was agreed to be a key problem, especially in older children and adults.

**Potential interventions in autism spectrum disorders**

It was recognized that there was no clear evidence of efficacy of pharmacological interventions on long term prognosis, and only weak evidence for behavioural interventions, with no evidence of specificity. Existing pharmacological studies had little underpinning neurochemistry, and mainly dealt with comorbidities, whose pathophysiology was better understood.

There was recognition that some interventions may elucidate primary and secondary processes of the underlying pathology of ASDs, but that this was not true in all cases. Whilst agreeing that complex intervention methodology was important to consider, it was not clear that it was always appropriate, and simpler more focussed studies addressing a single treatment may be more helpful.

Interventions for very young children needed to be considered within the relevant context. Parents of children with disabilities needed information, a key worker with autism expertise, and social support, etc. The National Autism Plan for Children had specified 15 hours a week autism specific intervention. There was some debate as to the appropriateness of evaluating “intervention packages”, or rather to look at the specific content of potential interventions in terms of the core features of ASDs (communication, social interaction, management of repetitive behaviours, and management of habit patterns).

It was recognized that there was a range of potential interventions that could be designed and evaluated, including educational provision, social skills, psychiatric treatments (including psychological intervention and psychopharmacology), dietary and intestinal floral interventions, and other therapies (e.g. speech & language therapy; occupational therapy; physical therapy; individual or group psychotherapy; vocational skills development; and independent living & leisure skills).

General interventions may be common to many disabilities, whereas specific interventions might focus on family support/ interventions/ information, or child focussed interventions/information.

The benefit of targeting treatments at associated co-morbidities was discussed. For example there are conditions that could amplify the ASD (such as epilepsy or depression), as well as co-morbid symptoms, such as sleep disturbance, obsessions & compulsions, attentional disturbance, bowel problems, aggression, self injury.
Research priorities and Promising interventions

The research strategy that had been developed as part of the MRC Review mapped well onto the study of interventions for ASDs. There was a need to build on UK strengths, and to facilitate lay & service provider participation within researcher-funder partnerships. It was particularly necessary to reduce the apparent disparity between the priorities of scientific research & those of individuals with ASDs, their families and carers. There was a need to investigate potentially modifiable environmental risk factors, and for service evaluation.

Participants at the workshop identified a number of areas that they considered could be considered as the most appropriate areas to evaluate, being (in no priority order): dietary interventions, “early intervention”, and the natural history of ASDs including co-morbidities. It was acknowledged that there may be a need to consider an appropriate sequence of interventions (e.g. diet, followed by behavioural, then social interventions or management strategies).

Cross-cutting themes that occurred during discussion included:

- The importance of proper controls, which might mean matching for IQ, and the possibility of compensatory mechanisms (especially in higher-functioning older children and adults).
- The lack of understanding of the normal cognitive and structural developmental trajectory, and how this progressed into adulthood.
- The potential confounding issues surrounding co-morbidities in individuals with autism spectrum disorders.
- The need to link research to service provision.

The meeting concluded with a short presentation by Dr Chris Watkins (MRC Autism Programme Manager) of the MRC and its funding schemes. An explanation of the application procedure was described.