

Clinical trials and tribulations: the MASCOT study



EDITOR'S
CHOICE

Warren Lenney,¹ Sophie Perry,² David Price³

Following the 1994 *Lancet* paper showing benefits of long-acting β -agonists (LABAs) in adults with asthma,¹ British Paediatric Respiratory Society surveys have consistently recommended undertaking similar studies appropriately designed for children. Adult outcome measures should not be extrapolated into childhood, which explains why early studies indicated LABAs may be less helpful in children.² With the advent of the Medicines for Children Research Network (MCRN) in 2004, the Health Technology Assessment (HTA) put out a call for children's medicines studies in 2005. The Management of Asthma in School Children On Therapy (MASCOT) study was funded in January 2006 pending Pharma approval to supply the medicines (fluticasone, fluticasone-salmeterol combination treatment and montelukast) as National Institute for Health Research funding does not include excess treatment costs. This task took 12 months including lengthy discussions with Merck, Sharp and Dohme (MSD) about methodology and statistics.

THE MASCOT STUDY

The protocol required 900 children to use inhaled corticosteroids (ICS) for a 4 week open run-in followed by 48 weeks (double blind, double dummy) taking ICS, ICS plus LABA or ICS plus montelukast. The primary outcome measure was the exacerbation rate. The HTA funded MASCOT research costs. MSD and GlaxoSmithKline (GSK) agreed to supply medication. There was a delay in appointing a trial coordinator to oversee the 13 sites which had

readily agreed to participate. The lengthy task of writing the protocol to EU standards (in addition to the original protocol designed for HTA application) was new and baffling to many of us, as was the preparation and submission of the Clinical Trials Authorisation.

STUDY PROGRESS

- ▶ No medicinal National Health Service (NHS) packaging company could undertake the complex arrangements to receive and package the medications and distribute them to the sites. So in December 2007 we returned to the HTA to request additional commercial funding for this, which increased the study budget to £1 million.
- ▶ In December 2007, GSK ceased production of metred dose inhalers (MDIs) for research studies. MASCOT therefore needed to change to powder inhalers. Some principal investigators were unhappy with this, but there was no alternative.
- ▶ In February 2008 the Multicentre Research Ethics Committee (MREC) questioned the study statistics and were unhappy with one study arm containing ICS alone. Answering the MREC's questions and making the alterations they requested took 3 months before approval was finally granted (with no substantial protocol change!).
- ▶ The protocol was now in its fourth (approved) version, each version having to be approved by all 13 R&D departments and all Primary Care Trusts (PCTs) involved.
- ▶ Most of the 13 research nurses took up their post by June 2008 (2 ½ years after initial study funding).
- ▶ Montelukast tablets arrived in August 2008. Their expiry date was December 2008! To extend their shelf life, stability data were required from MSD who were unable to devote time to this.
- ▶ New medications were promised by October 2008 but they did not arrive until early 2009. By then the GSK inhalers were close to expiry so new batches were needed.

- ▶ All medications were promised by January 2009, so we decided to begin recruiting patients. When the medicines did not arrive, the six patients recruited had to be withdrawn, leading to disappointment and disillusionment within the MASCOT team.

The above eight obstacles were not of the study team's making and delayed the study opening by at least 18 months.

RECRUITMENT ISSUES

The study re-opened in May 2009 but recruitment was slow:

- ▶ Children in secondary care were mainly too young for the study (preschool age) or were already receiving add-on therapy.
- ▶ Contact with primary care was complex, with few practices confident about recruiting or undertaking studies in children.
- ▶ Approximately 30 children per average-sized general practitioner (GP) practice were identified as potentially suitable for study inclusion. Letters were posted but only one or two of the 30 families replied and most did not meet the inclusion criteria. The study researchers, who were not part of the primary care team, were not allowed to approach parents directly.
- ▶ Children suitable for inclusion from research-aware practices were often receiving add-on therapy.

OTHER CHALLENGES

- ▶ The Department of Health and the National Information Governance Board (NIGB) differed as to who could access patient notes in secondary care. This made it very difficult to identify eligible patients.
- ▶ Families agreed to participate and then frequently failed to attend study appointments.
- ▶ Busy clinical staff felt unable to prioritise time for research.
- ▶ The complexity and variability of communications between the newly developed medicines for children, primary care and comprehensive research networks proved very trying.
- ▶ To obtain service support costs, each Comprehensive Local Research Network (CLRN) had a different application process and form for the same request.

PLANS TO IMPROVE RECRUITMENT

We met the study nurses in June 2009 to develop new recruitment strategies.

¹University Hospital of North Staffordshire and Keele University, Academic Department of Child Health, Stoke-on-Trent, Staffordshire, UK; ²Medicines for Children Research Network Clinical Trials Unit, Institute of Child Health, Alder Hey Hospital, Liverpool, UK; ³Respiratory Primary Care, Centre of Academic Primary Care, University of Aberdeen, Foresterhill Health Centre, Westburn Road, Aberdeen, UK

Correspondence to Professor Warren Lenney, University Hospital of North Staffordshire, Academic Department of Child Health, Stoke-on-Trent, Staffordshire ST4 6QG, UK; warren.lenney@uhns.nhs.uk

Between October 2009 and January 2010, WL and SP visited all 13 centres to understand local issues. WL and SP contacted other potential UK centres where staff understood childhood asthma and had good communication among their research networks. Nineteen centres were deemed suitable, but more funding was needed. A meeting was requested with the HTA in November 2009; we submitted a detailed business case to include the new sites, without which the study would fail. Further protocol revisions included new innovative recruitment strategies in both primary and secondary care.

HTA met with the MASCOT team in February 2010 insisting on a doubling of recruitment into the double-blind part of the study by May 2010. No money was available for new centre inclusion.

PROGRESS

Huge efforts were devoted by MASCOT teams; immense numbers of letters, files and other documentation were generated to meet governance requirements. Many new recruitment strategies were developed and initiated. By May 2010, 168 children had entered the run-in (900 expected) with 65 children randomised into the double-blind arm (450 required). A total of 6600 study invitation letters had been posted to families; 450 responses were received; 1038 follow-up letters were sent; 83 responses were returned. One hundred and fifty-five phone calls to families were made in five general practices—no child was recruited as a result. EMIS computer 'pop-up' reminders specifically designed to trigger when a child met MASCOT entry criteria were installed in six general practices between March and June 2010. One patient was recruited using this method. In the 3 months from March to May 2010, many more patients and families were contacted than previously because of new recruitment strategies. The number recruited into the run-in more than doubled, but randomisation into the double-blind phase increased little as patients were often asymptomatic at

the end of the run-in. There was no clear explanation for this as inclusion parameters were unchanged. The HTA closed the study in June 2010. The new recruitment strategies were not really given sufficient time to demonstrate their effectiveness. The MASCOT team had hoped to pursue these through the autumn when symptoms for childhood asthma are most frequent.

COMPARISON WITH THE USA

GSK and MSD were approached to supply medications for MASCOT and for the American BADGER study³ at the same time. The BADGER study was completed and published in the *New England Journal of Medicine* in March 2010. Asthma prevalence in the UK is equivalent to or higher than in the USA, yet our study was dogged by bureaucratic, communication, governance and recruitment issues. In the USA specialist doctors follow their own patients through the primary and secondary care setting, which may enhance recruitment and reduce bureaucracy.

OPINION

Questions which could be important for future UK study development and success are highlighted below.

Research questions

- ▶ What type of study would parents and children wish to see developed?
- ▶ Can study set-up time be reduced?
- ▶ Are the Research Network systems flexible enough?
- ▶ What percentage of global commercial studies take place in the UK compared with 10 and 20 years ago?
- ▶ Can research involving secondary and primary care be simplified?
- ▶ Can research governance be streamlined?
- ▶ How do we focus more on outcome not process?

Sixteen years have elapsed since the publication of LABA benefits in adults. Prescribing practice in UK children has changed despite no good evidence-based studies. Recent articles have even suggested an overuse of combination treatment.^{4 5} Research study set-up in the UK is bureaucratic and protracted. Studies requiring working across various networks (MCRN, Primary Care Research Network (PCRN), CLRN, PCTs, Hospital Trusts, GP practices) are difficult as priorities differ. Research is not an accepted part of clinical practice in the eyes of many busy clinicians. Parental priorities revolve around work, school, after-school activities, etc. and do not seem focused on clinical research.

Recruitment of children into clinical studies poses specific problems different from those of adults. This is particularly true in common conditions where few studies are taking place at present.

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Competing interests None.

Ethics approval This study was conducted with the approval of the MASCOT study approved by North West MREC 2008.

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