Evidence Notes

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Welcome to the seventh issue of *Evidence Notes*. This article is the first of three focusing on pragmatic controlled trials (PCTs) and their potential future role in decision making by regulatory and HTA agencies. Part 1 examines the place of PCTs in pre-approval medicines development. Part 2 will focus on the concept and status of the Adaptive Pathway initiative (formerly Adaptive Licencing), in which inclusion of plans for collection of real-world data is a key component. Part 3 will report on results and regulatory/HTA impact of the world's first pre-approval PCT (the Salford Lung Study), once data are available.

With this breakthrough study in mind, we are delighted to have had the opportunity to interview Dr David Leather of GSK, one of the leaders of the Salford Lung Study, about his experience to date with the study.

The Role of Pragmatic Controlled Trials (PCTs) in Pre-Approval Medicine Development

The principle role of drug regulatory agencies is to ensure that drug approval is based on high standards of efficacy and safety. This relies on data from studies designed to rigorously determine cause and effect i.e. randomised controlled trials (RCTs) – sometimes referred to as "explanatory" trials. RCTs typically aim to eliminate bias, have narrow, well-defined patient populations and treatment regimens, and often compare an experimental treatment with placebo. RCTs are therefore conducted under "ideal" conditions and, whilst these features confer high validity, the design choices for pivotal RCTs often result in data that are not easily generalizable to the population treated in clinical practice.

In contrast, PCTs are designed to explore whether an intervention works in clinical practice thereby addressing an issue of key importance to patients, clinicians, payers and policy makers.[1, 2] The general aim in designing a PCT is to preserve some of elements of rigour (e.g. randomisation) but to maximise the generalizability of the data by including, for example: broader patient populations, diverse settings, comparator treatments, flexibility of treatment (e.g. switching/dose adjustment), and a wide spectrum of clinically meaningful outcomes (e.g. patient-reported outcomes). In reality, the distinction between RCTs and PCTs is not "all or nothing". There is an explanatory-pragmatic continuum in both the type and degree of pragmatism that can be incorporated into a trial design (see below for further details).

In focusing their reviews on RCTs, regulatory agencies and Health Technology Assessment bodies (HTAs) address specific uncertainties (e.g. efficacy in a homogeneous clinical trial population) and ignore others (e.g. effectiveness in the broader patient population). Since PCT data is typically generated post approval, HTAs may only have RCT data on which to base their initial decisions. Yet these agencies need to be confident that when a new treatment is used in clinical practice it is not only safe and efficacious but is also effective (and cost-effective) in the real world, over and above existing standard of care.

To better deal with this evidence gap, regulatory agencies are currently investigating creative and flexible ways to develop medicines. For example, the European Medicines Agency (EMA) has launched the Adaptive Pathways (AP) initiative. This will be discussed in detail in Part 2 of this series but, in essence, it involves a prospectively planned, flexible approach to drug regulation with iterative phases of evidence generation, regulatory evaluation and license adaptation. It is envisaged that initial approval will be in a restricted patient population (to allow rapid market access), followed by an increasingly wider population. The generation of data from real-world studies (e.g. PCTs in wider patient populations), based on parallel scientific advice with EMA and HTAs, will be considered an essential part of the early planning process to allow prompt label adaptions.[3-6]

Whilst there are many discussions on the role of PCTs in a future drug development paradigm, presently there are no specific guidelines on incorporating PCTs into regulatory submissions.[6-9] In the case of HTAs, although they will accept and review non-RCT data, many conform to the evidence hierarchy ("available guidelines often clearly state that non-RCT evidence will be regarded circumspect"[6]). In fact, only 10 out of 3,590 HTA assessments from 9 HTAs included a PCT (all post-approval).[10] In some cases, the PCT data was viewed unfavourably because the results conflicted with RCT data (yet this might be expected if, for example, adherence in PCTs differs from RCTs). In others, although the overall evidence base was accepted, it is unclear how much influence the PCT had on the assessment.

As mentioned, there is balance in the type and degree of pragmatism that can be incorporated into a trial design. To help trial designers explore the extent of pragmatism they may wish to adopt a tool known as PRECIS (Pragmatic Continuum Indicator Summary[11-12] has been developed (now updated to PRECIS-2[13]). This uses a wagon-wheel approach to defining the type and degree

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A very pragmatic trial

Flexibility of the Comparison Intervention
Practitioner Expertise (Experimental)
Practitioner Expertise (Comparison)
Flexibility of the Experimental Intervention
Follow-up Intensity
Eligibility Criteria
Outcomes
Primary Analysis
Participant Compliance
Practitioner Adherence
E

A very explanatory trial

Flexibility of the Comparison Intervention
Practitioner Expertise (Experimental)
Practitioner Expertise (Comparison)
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Follow-up Intensity
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E

Eligibility
Who is selected to participate in the trial?
Recruitment
How are participants recruited into the trial?
Primary analysis
To what extent are all data included?
Setting
Where is the trial being done?
Primary outcome
How relevant is it to participants?
Organisation
What expertise and resources are needed to deliver the intervention?
Follow-up
How closely are participants followed-up?
Flexibility: adherence
What measures are in place to make sure participants adhere to the intervention?
Flexibility: delivery
How should the intervention be delivered?

of pragmatism across a variety of domains including: recruitment, setting, eligibility criteria, flexibility of delivery or adherence of the intervention, primary outcome etc. Figure 1 shows the degree of pragmatism at the extreme ends of the explanatory-pragmatic continuum based on the domains of the original PRECIS tool and Figure 2 shows the domains of PRECIS-2.

In 2015 the Innovative Medicines Initiative (IMI) GetReal Project held a workshop including pharma, regulatory (EMA) & HTA (NICE) agencies, academia, patient organisations, physicians and payers to understand stakeholder views on PCTs conducted prior to authorisation.[16] In general, key conclusions/recommendations included:

- Identify the effectiveness/efficacy gap to determine if PCT required; PCTs have a clear role where efficacy in RCTs is not predicted to match effectiveness (e.g. due to patient characteristics, comorbidities, poor adherence)

- Create a development plan that plays on the strengths of RCT (internal validity) and PCTs (external validity i.e. generalizability); PCTs are not a replacement for RCT but a supplement

- Identify those pragmatic elements which may have the greatest impact if implemented early in a development programme

- Incorporate greater consultation (e.g. joint regulatory/HTA scientific advice) to help define relevant pragmatic elements, improve estimates of effectiveness and reduce uncertainty in decision making; and more patient input would improve acceptability

Table 1 provides examples of where pre-approval PCTs may be beneficial.[2, 9-10, 16, 17-20] In addition, some key barriers to the use of pre-approval PCTs are shown in Table 2.[6, 14, 16]

Table 1: **Circumstances where pre-approval PCTs may be beneficial vs less/not beneficial**

Beneficial	Less/Not Beneficial
Medical conditions in which patient characteristics or patients behaviour (e.g. degree of autonomy or "self-treatment") are likely to impact treatment effects (e.g. diabetes, arthritis, asthma etc.)	Medical conditions in which standard (RCT) trial conditions don't differ much from real practice (e.g. oncology)
Where relative effectiveness estimates based on RCTs may be challenged by regulatory or HTA bodies (e.g. where patient populations are non-representative)	Potential for greater risk in pre-approval setting where efficacy, AEs and/or co-morbidities may be less well known
Where RCTs may not be feasible (e.g. orphan diseases)	Drugs with a novel mechanism of action
When there is a wide variety of comparators or are used off-label	Head to head comparator studies
In chronic diseases with an absence of hard endpoints	Equivalence studies
In diseases where PROS are important	Where outcomes require special procedures
In diseases with high population heterogeneity	Where efficacy uncertain
In studies of preventative treatments in large populations	
Inform the design of pivotal trials	
Identify sub-populations with optimal risk-benefit profiles	
Determine natural history of the disease, patient populations etc.	

PRO = Patient Reported Outcomes

Table 2: **Key Barriers to the use of pre-approval PCTs**

Definitions	• Variable and contradictory definitions • "Real-life" may differ in different cultures/countries/health care systems
Guidelines	• Lack of specific best practice guidelines and harmonisation between stakeholders (esp. between pharma, RA's and HTAs) on methods, tools, analysis approaches etc.
Data	• Evidence hierarchy – if results are inconsistent with RCT data the latter are viewed more favourably; "clinical effectiveness is rarely solely determined (by HTAs) on the basis of real-world evidence" • Clinical uncertainty in the data (e.g. treatment switching leading to breakdown of randomisation; uncertainties over appropriate analysis etc.)

According to the authors, the Salford Lung Study in asthma and COPD is **world's first pre-approval Phase III randomised PCT**[21] and, although on-going, is a useful case study to explore.[21-25] The study was designed to compare the real-world effectiveness of novel vs existing treatments and was based on scientific advice from MHRA, NICE and the National Institute for Health Research (NIHR). Real-world evidence in both these conditions is important because it is difficult to extrapolate RCT data into real life due to issues such as age, co-morbidities or poor adherence. The key aims were to make the study as close to real-world as possible for an unlicensed medicine (e.g. heterogeneous patient population, patient experience as per practice, usual care in each arm, relevant endpoints) whilst maintaining scientific rigour (randomised, controlled, interventional). The study has its limitations (e.g. the Salford population or health care system may not be generalizable elsewhere) and is complex, expensive and logistically very challenging to conduct. However, it is ground breaking research and has already provided some useful learnings for future research (see Table 3).

Table 3: **The Salford Lung Study in Chronic Obstructive Pulmonary Disease (COPD) & Asthma**[21, 24-26]

Key Design Features	Limitations	Lessons learned
• Embrace heterogeneity with minimal exclusion criteria • Make patient experience as close as possible to usual care (e.g. minimal patient visits & procedures; prescribing as per practice) • Maintain scientific rigour: randomised, controlled • Data collected via an electronic health record (EHR) system connecting hospital, primary and secondary care practices and pharmacies • Robustness of real time safety data enables conduct in Phase III • Data reporting and analysis team are blind to patients' treatment. Patients & those directly involved in study conduct are not blinded.	• Open-label • Salford population may not be representative • Recruitment challenge in small participating region • Consent and the concept of taking an experimental medicine may make eligible patients reluctant to participate • Treatment switching may affect the benefits randomisation	• Systems to extract data from EHRs is complex, expensive & logistically challenging • Need to ensure quality and availability of data in EHRs is known prior to start • May not be possible to conduct in regions or countries without EHR and necessary infrastructure • Ensure data will have sufficient reimbursement benefits relative to other much less costly approaches

Conclusion

In focusing regulatory review exclusively on RCTs there is a continuing efficacy/effectiveness gap that hinders proper understanding of a medicines role in the broader clinical environment. One way to narrow this gap is to consider conducting real-world PCT studies earlier in development, prior to licence approval. The recent IMI GetReal project has provided useful insights from a wide variety of stakeholders to help understand their views on conducting such studies pre-authorisation (e.g. circumstances where PCTs may be beneficial, barriers to use etc.) and the Salford lung study, though still on-going, has shown that rigorously designed pre-approval PCTs can be operationalised despite some formidable logistical complexities. Other ways to harness real-world data as early as possible in development will be explored further in the next article by examining the EMAs AP initiative which will replace the "pre-approval" paradigm with an iterative approval process.

Now please read on to learn more about the Salford Lund Study from one of the architects of the Study, Dr David Leather of GSK, to whom we at Bridge, are very grateful for his time and thoughts (Please note that during the interview, Dr Leather often used the term "pre-licence RCT in everyday clinical practice" as opposed to pragmatic clinical trial).

Question and Answer Session with David Leather, Global Medical Affairs Leader, GSK

Q1: Can you describe the background environment that led to the development of the Salford lung study?

We were hearing calls from several important stakeholders that they needed more than just efficacy data in narrow, homogeneous patient populations.

Probably the most vociferous in this regard were the payers/HTA bodies. They felt strongly that the patients recruited into traditional RCT trials were not fully representative of those who would receive the medicine in the real-world. We know, for example, that in COPD and asthma less than 10% of real-world patients would be eligible for a traditional RCT because the other (non-eligible) patients tend to have a high incidence of co-morbid conditions, which can complicate interpretation of clinical trial findings. Patients with these primary care diseases are therefore also

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In a recent public announcement (24th May 2016) positive headline results from the Salford lung study in COPD have been confirmed, with the novel treatment showing a superior reduction in exacerbations versus usual care. Analyses are ongoing and will be subject of future publications and regulatory/HTA discussions. Further insights from this study will be explored in Part 3 of this series once the regulatory/HTA impact of the results is understood.

taking many associated concomitant medications whose use would be restricted in an RCT. Payers and HTA bodies were also increasingly reluctant to pay for new medicines in these disease areas when the incremental improvements in efficacy demonstrated in RCTs were not life extending.

Regulators too have an interest, particularly in being able to assess real-time safety data in a broad population of patients.

Other bodies expressing an interest in more generalizable patient populations included WHO, guideline writers and, most importantly, enlightened patient advocacy groups.

So, there was an evidence gap that needed filling, but we also realised the importance of generating robust effectiveness data.

Q2: Why did you decide that a pre-licence pragmatic study was the best way to address this evidence gap?

First and foremost we needed to generate clinical trial data that would blend the requirements of scientific rigour – i.e. prospective, randomised, controlled – with a design in which the experience of a representative patient population would closely mimic that of everyday clinical practice.

There were a number of factors that made Relvar a good candidate. Apart from a good efficacy and tolerability profile, we expected its dosing and device delivery advantages to produce outcome benefits associated with high adherence. These would likely be observable in an everyday clinical practice setting but perhaps not in an RCT where adherence would be strictly controlled.

We also knew that for the data to have the most impact around the time of launch, the key question would be whether we could conduct the study pre-licence.

GSK were hugely supportive despite the high at-risk investment because they recognised the evidence need and that a pre-licence trial with Relvar

conducted in everyday clinical care would establish a quality standard and an operational and governance framework that could be applied to other medicine development programmes.

Q3: What did you think would be the impact of the study on payers and on regulators?

This is unknown territory. For both stakeholders, pragmatic trial data doesn't fit with the established evidence hierarchy. How they will interpret the data will only become clear with time and it may be a challenge.

But what is clear is that payers are interested and want to understand how to deal with the data. Although this will be an entirely new experience for them, their view was basically "bring us a dataset and let us understand how it fits". In short, the world is waiting for a study.

One of the best things we did was to seek joint MHRA/NICE guidance. This turned out to be a very positive, proactive and "inspiring" experience. NICE were very keen on the study and offered ideas for broadening the population and it was good that the regulators were there to hear and contribute to the discussion at the same time.

Q4: What were the key challenges in getting the study started?

There were a number of significant challenges:

Firstly, establishing a comprehensive Electronic Health Record system that links primary and secondary care facilities and every high street pharmacy to generate data in near- real time. This was very important, especially for safety data with an un-licensed product. It was also crucial in being able to limit the number of patient visits to make it more like clinical practice rather than a study. Such a system was available in Salford (perhaps currently the only place globally where this is possible) but it still had to be adapted to capture additional data sources and meet clinical trial standards.

Secondly, it was difficult getting GPs, who are not academic researchers, to recruit their own patients. We also had to enlist every high street pharmacist. Ultimately we had to train approximately 3000 people in Good Clinical Practice!

Thirdly, there were regulatory and ethics challenges. For example, whilst an RCT conducted in everyday clinical practice needs to limit any barriers to recruitment, the amount of patient information required to meet ethical standards for consent – especially involving an experimental medicine – can be a barrier.

Finally, there were significant operational and IT challenges. Although Salford GPs were already using an electronic health record system, this was not developed to meet the needs and standards of a clinical trial. For data extraction and analysis new software had to be developed and QC'd. Not all the pharmacies were using the same computer system and so work-arounds had to be developed.

Q5: What are your key learnings regarding implementation of this study?

Given the pioneering nature of a pre-licence RCT in everyday clinical practice, the vital initial ingredient was support from the top of the organisation. This novel approach was high risk but also potentially high gain and they were extremely supportive.

In terms of the implementation though, I would say that the most fundamental ingredient was the collaborative way in which all those involved in the study came together to achieve the goal. It would be easy for a study such as this to founder but there was a true partnership and all played their part in finding solutions to problems. This was helped by us setting clear goals and having appropriate governance and structures such as a direct hotline for participants to reach decision makers.

Another key aspect is the role of the patients and their relationship with the GP. I would like to think that through the creation of a culture of interest in the

study, the patients felt like equal partners in the project and I would personally like to express my thanks and recognition for their contribution towards the successful implementation of this study.

Q6: Do you think this study is transferable to other UK locations or other countries?

Within the UK I would say that the situation is evolving. Industry needs to seek out and develop capabilities in other cities but certainly there is no reason why this could not be done.

The UK may have a unique infrastructure, but again this may also evolve in the future.

The study was designed to reflect everyday clinical practice and includes a broad patient population including those with comorbidities and who are on polypharmacy. Even though there will be

demographic differences between the Salford population and other parts of the world the fact that there were very few exclusion criteria in the study means that the patients are more representative of the typical COPD patient than many other RCTs.

Q7: What are your hopes for this type of pre-label study in the future?

I believe this study will prove to be invaluable and will open the door to many more studies of this type. The study will help us learn how to implement similar studies and analyse and interpret the data. They won't be appropriate for all new chemical entities but there is a strong chance they will be important in the new adaptive licensing initiative in Europe and also provide a real-time platform for the management of safety data.

Q8: Any final thoughts and comments?

All in all, it has been an invaluable experience, well worth all the challenges and I would encourage others to give the approach serious consideration in their development plans.

Finally, I would like once again to express my sincere thanks to all the many partners and patients who contributed to this study.

Further information on this subject can be found in the references provided.

Dr Martin Jones PhD and Dr Paul Gandhi MD of Bridge Medical Dr David Leather MD of GSK (for the interview on the Salford Lung Study)

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