



Commissioning Framework for Experimental Treatments

Experimental and unproven health care interventions where published clinical effectiveness evidence is conflicting or of poor quality

NHS Leeds North Clinical Commissioning Group, NHS Leeds South and East Clinical Commissioning Group and NHS Leeds West Clinical Commissioning Group

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Commissioning Framework

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1 Definitions and background

Leeds Clinical Commissioning Groups (CCGs) NHS Leeds North CCG, NHS Leeds South and East CCG and NHS Leeds West CCG Individual Funding Request (IFR) policy sets out the process via which evidence of clinical and cost effectiveness to inform a judgement about an individual funding request is sought. Often there is high quality evidence (good Randomised Controlled Trials, Systematic Reviews, Meta analyses, NICE Guideline, or equivalent) against which to assess a funding request.

Inevitably, there are scenarios where the evidence is weak, patchy, incomplete and conflicting. It is common, particularly for IFRs relating to rarer diseases, for there to be limited published evidence, often of poor methodological quality. Frequently the evidence base consists of a number of case reports or case series; particularly for uncommon surgical techniques and off label medicine use.

In such circumstances, the level of clinical consensus for use of that treatment may range from weak (eg a single clinician requesting a treatment as they read about it in a journal, or because a patient requested a treatment based on their own research), mixed (eg some support, some don't support use in that indication) or strong (eg consistent support across multiple clinicians and possibly widespread use of that treatment).

Regardless of whether there is evidence (of any quality) decision still needs to be made on whether Leeds CCGs will fund a treatment that has been requested.

1.1 Purpose of this document

This document is intended as an aid to decision making. It should be used in conjunction with Leeds CCG policies on Individual Funding Requests and associated decision making frameworks.

This document clarifies the circumstances under which a treatment may be considered experimental, unproven or of uncertain clinical effectiveness. The document also provides guidance as to how poor quality evidence should be interpreted by the CCGs in making a funding decision (a decision to allocate taxpayers money to funding a specific treatment, with the consequent benefits / risks and opportunity costs; this is viewed as distinct from a clinical decision).

This document should be used alongside Leeds CCGs' policy on interventions targeted to deliver maximum health benefit; that sets out the CCGs approach to funding interventions that are part of the NICE IPG programme.

2. LEEDS CCGs *guidance on experimental and unproven treatments.*

2.1 This guidance applies to any patient for whom the Leeds CCGs are the Responsible Commissioner.

2.2 Except as set out in points 2.3 onwards:

2.2.1 Leeds CCGs do not routinely fund treatments which are judged experimental or not to be of proven effectiveness; and

2.2.2 Funding for individual patients or groups of patients within poorly designed trials will not be supported.

2.3 Where the evidence is base is poor, Leeds CCGs will encourage patients to be entered into appropriate trials. Although the CCGs have the power to conduct, commission or assist the conduct of research into specified matters and a duty to promote research and the use of evidence obtained from research, it would be unusual for Leeds CCGs to directly sponsor a trial. If there is doubt, a clinician should discuss such cases with the appropriate CCG prior to consenting a patient into a trial.

2.4 Leeds CCGs may give consideration to supporting experimental treatment or off label use for rare clinical situations for which good quality clinical trials are considered impossible. These will be considered under the individual funding request. These will be identified on the basis of:

- the incidence of the clinical condition / circumstance;
- the nature of the intervention;

- the nature of any clinical research.

In general, Leeds CCGs will commission new and existing orphan drugs within the same framework as for other treatments; unless otherwise directed by NHS England.

2.5 When a case has been identified under paragraph 2.4 NHS Leeds will consider the following:

- the potential benefit and risks of the treatment;
- the biological plausibility of benefit based on other evidence;
- an assessment of value for money;
- the priority of the patient's needs vis-à-vis other competing demands.
- How long benefits will take to be realised, bearing in mind time taken to assess the intervention, implement changes to affect a change in practice, and time taken for the intervention to become effective.

2.6 The clinician will be expected to provide as much information as possible about the treatment, relevant research upon which the claim for biological plausibility of the treatment is based, and costs, as well as clinically relevant information on the patient. In addition, the clinician will identify the clinical markers and clinical outcomes that will be monitored to assess treatment response.

2.7 When a case has been identified under paragraph 2.4 the funding options which Leeds CCGs will consider are:

- Not to support.
- Support application for funding to organisations such as NIHR for a trial of treatment but make ongoing treatment subject to the demonstration of clinical benefit for the individual patient using criteria agreed in advance with the clinical team.
- Fund directly

2.8 In all instances, contribution to any relevant clinical database or population registry which is operating will be an additional condition of approval of funding for the treatment.

2.9 Providers will not be paid for any activity with regards this framework which has not been approved in advance.

3 Issues for consideration by IFR panels when considering requests for treatments that might be considered experimental

A number of factors that might be considered important when assessing whether a treatment should be viewed as 'experimental' warrant further investigation.

a) Defining 'Experimental' – some general parameters

Experimental and unproven treatments are medical treatments or proposed treatments where there is no established body of evidence to show that the treatments are safe, effective and cost effective. The reasons for this may include one or more of the following:

- the treatment is still undergoing clinical trials and/or yet to undergo a phase III clinical trial for the indication in question
- there are no relevant articles published in the peer-reviewed journals available on the treatment for the indication in question
- the treatment does not have approval from the relevant government body
- the treatment does not conform to usual clinical practice in the view of the majority of medical practitioners in the relevant field
- the treatment is being used in a way other than that previously studied or that for which it has been granted approval by the relevant government body
- The treatment is rarely used, novel, or unknown and there is a lack of authoritative evidence of safety and efficacy.
- the evidence is not yet available for public scrutiny
- There is some evidence to support a case for clinical effectiveness but the overall quantity and quality of that evidence is such that the commissioner does not have confidence in the evidence base and/or there is too great a measure of uncertainty over whether the claims made for a treatment can be justified.

It is very difficult to define a clearly objective set of criterion or weights that determine how the above factors will be used in making a judgment that a treatment is experimental. Judgments will be made by the CCGs in conjunction with the relevant specialty clinicians. Many of the conflicting ethical and evidential standpoints are not easily resolvable. Leeds CCGs will try to act in a rational and reasonable manner when making such decisions, balancing all relevant factors.

b) Interpreting Poor Quality Clinical Effectiveness Evidence

Published evidence of clinical effectiveness, that is methodologically high quality, is a principal determinant of whether an intervention might be considered experimental by NHS Leeds.

It is expected that a clinician requesting treatment through an IFR, or suggesting a new funding policy will submit appropriate clinical effectiveness evidence, against which the request can be considered.

This section gives further clarity on **how** judgments are made, particularly about poor quality clinical effectiveness evidence. It has obvious application to IFRs, policies pertaining to specific treatments and service developments more broadly.

In general, the task of appraising submitted evidence; testing its validity and quality and informing the broader process of making a funding decision is undertaken by Local Authority Public Health specialist staff.

It is rarely possible to perform full systematic reviews of all available literature, for each treatment requested. Literature will be scanned by appropriately trained experts and key studies highlighted and appraised using standard tools. Consideration will be given to study design and study quality in line with established practice.

This process of appraisal is relatively straightforward where there is a Health Technology Assessment (NICE or equivalent), a systematic review (Cochrane or other), an evidence based clinical guideline (NICE or equivalent), or good quality randomised controlled trials.

It is common that the evidence of clinical effectiveness presented is a number of case reports or case series; or other forms of observational data. These can be difficult to interpret, as observational data is prone to a large number of biases (that are inherent in the research design) that can skew an interpretation of the true effect size. These can be characterised as:

- publication (only report good findings),
- selection (only recruit those most likely to respond),
- exclusion (eliminate non responders from the write up),
- observation and reporting (if I know who is being treated as is likely in an unblinded observational study, I will be more watchful for any improvement and may over-interpret)
- preference will be given to studies carried out in a cohort similar to the population within this PCT

Often this bias is hard to quantify as there is no comparator group, it is thus not possible to eliminate placebo effect, unknown confounding variables or natural history effect from the findings – thus making it even harder to have confidence that the results reported are a true treatment effect. Multiple case reports or case series often report on a very heterogenous (and often carefully selected) population; this makes inference harder still. Without a detailed and technical analysis on each of the case series considered in a decision about a particular treatment (which simply isn't possible within resource constraints), observational studies can (and frequently do) overestimate the treatment effect size (often by a considerable margin).

If no available comparators exist, then key aspects of natural history (such as survival rates at different time intervals if untreated) may be considered.

There are a wide number of other methodological issues inherent in the design of observational studies that makes interpretation of results on effect size and generalisation to another population problematic. Proposed treatments that rely on observational studies as evidence of clinical effectiveness are more likely to be considered experimental.

A particular difficulty arises when there is a disproportionate

- number of published studies in relation to:
- different subgroups of patients treated with the same procedures
- different devices used for the same procedure, or technical variations of a procedure
- different outcomes (for example, some studies reporting only efficacy and some only safety outcomes; some studies reporting quality-of-life outcomes, others not).

Where evidence of efficacy is conflicting or mixed, or where the published studies cover a heterogeneous population or a wide range of outcomes; particularly in circumstances where the methodological quality of evidence is poor, NHS BA may choose to prioritise a particular subgroup of studies, chosen to provide a balanced view of the evidence; or split an evidence review into subgroups (being mindful of the additional resource this will require).

Evidence will be selected and considered; specifically focusing on study designs that are least likely to be biased in their findings.

A number of other considerations are taken into account when considering the available clinical evidence

- **Study design.** Studies from the top of the evidence hierarchy will be preferred to studies of lower methodological quality.
- **Study size.** Preference is given to larger studies; they are more likely to provide accurate estimates of efficacy and safety.
- **Follow-up length and completeness.** Priority is usually given to studies with longer and more complete follow-up.
- **Patient-focused outcomes** - as opposed to surrogate outcomes - are considered particularly important when judging the efficacy of a procedure. Evidence that a procedure reduces tumour size carries less weight than evidence about clinical benefits such as enhanced survival and/or improved quality of life.
- **Safety** - studies that systematically report adverse events are considered important. Safety outcomes are often not well addressed in randomised trials. Large numbers of treated patients are required to reliably detect uncommon yet serious adverse events. Large case series, surveys and registers may provide valuable information, and case reports of rare complications may also prove useful and are given prominence, particularly when there is concern about the potential for rare but important complications. Although these sources often lack denominator data to substantiate incidence calculations, they provide qualitative information that can be highly relevant.

Unpublished evidence, including conference abstracts, will rarely, if ever, be considered in making judgments about clinical effectiveness.

Evidence submitted direct from manufacturers, unless published in a peer reviewed journal, will rarely, if ever, be considered in making judgments about clinical effectiveness

c) **Contributions from clinician advisors**

Leeds CCGs will seek contributions from specialist clinical advisors in discussing IFRs and commissioning policies. The extent to which this is undertaken will depend on the number of similar cases that have been considered in the past; and the level of detail in the submission. Invariably, this will be evidence taken from the clinician requesting the treatment.

New treatments often have potential benefits and, importantly, risks that are not yet fully described in the scientific literature. Clinical advisers provide insight into these aspects of a treatment, sometimes supported by accounts of their clinical experience, which complement the published evidence, particularly when this is limited. Clinical advisers will also need to identify emerging evidence.

d) **Rarity of disease and strength of clinical evidence**

Whether it is fair to discriminate, on the grounds of published evidence of clinical and cost effectiveness, against a person with a rare condition over a person with a common condition is an unresolved ethical question in the allocation of NHS resources. A principle of equity is deeply enshrined into EU thinking, and Law “.....not disadvantaged due to rarity of disease from which they suffer” (from EU a legal framework and economic incentives to aid development of treatments for OD). This does not, however, guarantee commissioning of a drug.

For treatments of rare diseases or rare manifestations of common diseases, it is often suggested that randomised controlled trials (RCTs) are often not available – and that non-randomised controlled trials and case series studies may therefore be the main sources of data for some procedures.

Developing a drug for any disease is often a very expensive process and when a disease is rare, the manufacturer will have fewer patients to ‘spread’ the cost of development. This will inevitably be reflected in a higher price, this is then reflected in cost effectiveness analysis. Whilst the issue of cost effectiveness is pivotal it is not absolute, however, to contend that it is not possible to do clinical effectiveness research in such circumstances is untrue.

Thus even if a disease is rare, Leeds CCGs would still expect to see evidence of clinical effectiveness in order to determine whether it considered a treatment experimental or not.

The CCGs may choose to develop a specific policy on 'rare diseases'. As a rule it is recommended that 'rare diseases' are considered within the same framework as all other treatments.

e) Place in pathway, availability of therapeutic alternatives.

The proposed treatment should be in the context of an agreed pathway of care. As a minimum this pathway should be:

- Informed by appropriate evidence of clinical effectiveness
- agreed by clinicians within that provider
- part of a treatment guideline for that particular condition

preferably, the proposed treatment should be:

- part of a national clinical guideline, NICE or equivalent.
- agreed by clinicians from the broader clinical community in the region, or national
- supported by the clinical MDT
- commissioner agreed.

f) Addressing the difficult and not easily resolvable ethical and exceptionality tensions

- Consideration should be given to circumstances where there are no therapeutic alternatives, and the consequences of not funding a treatment.
- Consideration should be given to the overarching decision making Leeds IFR policy around 'rescue' and 'salvage' treatments. One could state that there is always an alternative (best supportive care)
- There may be reputation risk issues to consider with not funding 'end of pathway treatments'
- We should consider exceptionality in this context. Especially where there is no general policy for that particular treatment, is a request:
 - a) Exceptional to the general population
 - b) Exceptional to the population with that disease or condition
 - c) Exceptional to the population with severe manifestation of that disease
 - d) Exceptional to the population with severe manifestation who have not responded / contraindicated to all the usual NHS commissioned therapies (ie within the NHS commissioned pathway, most often covered by tariff)

g) Incomplete or ambiguous clinical evidence

It is common for the clinical evidence supporting use of a treatment to be incomplete, because a medicine is new and long-term clinical trials have yet to be completed, its potential cost is difficult to assess, or it is an off-label or unlicensed use. Clinicians frequently request use of a treatment which does not have the benefit of evidence from extensive clinical trials, but which he, or she believes will assist their patient. The matter must be considered by Leeds CCGs according to their IFR policy. As the Court of Appeal said in *R v N Lancashire HA, ex p A, D & G* (1999):

...the mere fact that a body of medical opinion supports the procedure does not put the health authority under any legal obligation to provide the procedure... However, where such a body of opinion exists, it is...not open to a rational health authority simply to determine that the procedure has no proven clinical benefit while giving no indication of why it considers that is so.

h) Effectiveness v efficacy

Effectiveness means the degree to which objectives that have been identified in advance are achieved. In the NHS *clinical effectiveness* is a measure of the extent to which a treatment achieves pre-defined clinical outcomes in a target patient population. A treatment which is *efficacious* has been shown to have a beneficial effect in a carefully controlled and optimal environment. It is not always possible to have confidence that data from clinical trials will translate in clinical practice into the anticipated or any meaningful health gain for the target patient population of interest. This is the difference between disease orientated outcomes and patient orientated outcomes. For example a treatment might have demonstrated a change in some physiological factor which is used as a proxy measure for increased life expectancy but this relationship might not be borne out in reality.

Responsible clinical opinion in favour of a treatment is not decisive. If Leeds CCGs decide that they cannot support it, they must be able to explain why.

i) Medically necessary

HealthCare Definition of Medical Necessity for Physicians

"Medically Necessary" or "Medical Necessity" shall mean health care services that a Physician, exercising prudent clinical judgment, would provide to a patient for the purpose of evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- a) *in accordance with the generally accepted standards of medical practice;*
- b) *clinically appropriate, in terms of type, frequency, extent, site and duration, and considered effective for the patient's illness, injury or disease; and*
- c) *not primarily for the convenience of the patient or Physician, or other Physician, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

For these purposes, "generally accepted standards of medical practice" means:

- standards that are based on credible scientific evidence published in peer-reviewed, medical literature generally recognized by the relevant medical community;
- Physician Specialty Society recommendations;
- the views of Physicians practicing in the relevant clinical area; and
- any other relevant factors.

"Medically necessary" does not necessarily mean that a treatment will be funded.

One of the difficult decisions required by an IFR panel is to consider funding requests for treatments in circumstances where the patient's doctor (or dentist) has considered medically necessary a treatment that is not routinely funded within the NHS.

This does not give the IFR panel the authority to override a clinical decision, but it does give the authority to determine whether the NHS will pay for the treatment.

j) Endpoints

Following completion of the agreed treatment, a proportionate follow up process will lead to a final review appointment with the clinician where both patient and clinician agree that a satisfactory end point has been reached. This should be at the discretion of the individual clinician and based on agreeing reasonable and acceptable clinical and/ or cosmetic outcomes.

Once the satisfactory end point has been agreed and achieved, the patient will be discharged from the service.

Requests for treatment for unacceptable outcomes post treatment will only be considered through the Individual Funding Request route. Such requests will only be considered where a) the patient was satisfied with the outcome at the time of discharge and b) becomes dissatisfied at a later date. In these circumstances the patient is not automatically entitled to further treatment. Any further treatment will therefore be at the relevant Leeds Clinical Commissioning Group's discretion, and will be considered on an exceptional basis in accordance with the IFR policy.

Supporting evidence.

West Midlands Strategic Commissioning Group, Experimental and Unproven Treatments, Oct 2009

National Institute of Clinical Excellence. Interventional Procedures Programme. Methods guide. 2007

Legal and ethical aspects of local decision-making about medicines and treatments. *Chris Newdick, Professor of Health Law, University of Reading, NPC, 2009*

Bandolier. Bias <http://www.medicinesox.ac.uk/bandolier/band80/b80-2.html>. Accessed July 2013

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Delfini group. Problems with the Use of Observational Studies to Draw Cause and Effect Conclusions about Interventions http://www.delfini.org/Delfini_Primer_Problems_Obs_Interventions.doc Accessed July 2013

Cigna. Medical Necessity Definitions http://www.cigna.com/customer_care/healthcare_professional/medical/medical_necessity_definitions.html accessed July 2013

Appendix A: Version Control Sheet

Version	Date	Author	Status	Comment
Draft 1	4/7/13	J D Fear	Draft	Updated for Leeds CCGs
Draft 2	9/9/13	F Day	Final draft	Addition of cover page.
Draft 3	18.11.13	F Day	Final draft	Change of review date to april 2016, addition of endpoint
Draft 4	29.11.13	F day	Final draft	Addition of Providers will not be paid for any activity with regards this framework which has not been approved in advance.
				Addition of dissemination plan.
Final	18.5.15	F Day	Final	Reviewed policy dated 1.2.14, no amendments

Appendix B: Equality Impact Assessment

To ensure the Individual Funding Requests Policy and associated decision making frameworks for the Clinical Commissioning Groups in Leeds reflects due process for identifying the effect, or likely effect, of the policy on people with Equality Act protected characteristics – age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex, sexual orientation - and that the policy demonstrates due regard to reducing health inequalities, addressing discrimination and maximising opportunities to promote equality the following steps have been taken.

The update to the policy results from the iterative refresh process, and the requirement to make changes to care as indicated by an evolving evidence-base. This means that access is broadened as more treatments and interventions become available without the need for an IFR. There is no change to the underlying principles of the policy. In order for an IFR to be approved according to the core principles for managing Individual Funding Requests, it must be demonstrated that the patient's case is exceptional.

The following consultation and engagement activities have been undertaken. The evidence-based policy has been circulated to all GPs and secondary care consultants for comment, and has been made available on the internet to the public, along with Plain English patient information leaflets. The core principles for managing Individual Funding Requests in Leeds have been made available online for twelve weeks and disseminated through Patient Advisory Groups and Patient Reference Groups along with a cascade through the Community and Voluntary Service network. Feedback from all these sources has been collected by the Clinical Commissioning Groups. There is also an open and transparent approach to the processes of the decision making panel with an established mechanism for appeals.