

Guidance Note (GN/2)

The role of commissioners in the evaluation of individual treatments and the funding of clinical research

This paper sets out guidance for Primary Care Trusts and their relevant committees in considering applications for funding for treatments which may be classified as experimental or where further evaluation of treatment may be warranted.

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Background

There are a number of organisations driving and funding research, each of which has its own goals, interests and perspectives. The potential relationship between those responsible for planning and funding healthcare and research is complex.

The wider NHS has been an active player in R&D since its inception. Historically, those funding healthcare services have also funded research in specific instances. This position was strongly supported in the Peckham Report (circa 1990) that recommended that NHS organisations (both providers and ‘purchasers’) spend about 1-2% of their budget on research and development. In July 2009 a letter from the Department of Health set out the framework for entering more patients into clinical trials. The notion that commissioners should fund research is therefore not unusual, although the explicit commissioning of research by commissioning health bodies such as PCTs remains a relatively uncommon event.

In an environment where the need / demand for healthcare is greater than the ability of healthcare systems, including the NHS, to supply services, experimental treatments and the evaluation of treatment have to be undertaken sparingly, judiciously, responsibly and for clearly defined purposes.

Despite the emphasis and importance placed on the need to ensure that clinical practice and public policy is based on sound evidence, the NHS is under increasing pressure to introduce treatments earlier, on less evidence and *on demand*. Unfortunately the NHS has not been good at responding to these pressures. This difficulty is compounded by mixed messages that are given regarding access to treatments and a general misunderstanding of the constraints caused by limited healthcare budgets.

Another difficulty is the use and abuse of 'research' and 'evaluation' to avoid prioritisation decisions. By allowing a new intervention to be implemented in the guise of a short term study, but without plans to cease provision once the study ends, the intervention can become established without going through local prioritisation processes. Research and evaluation should *not* be seen as a tool to create early access to new and novel treatments in order to avoid any public display of rationing.

Clinical researcher time is a scarce resource as are the funds to support trials. As a result it is highly likely that important and desirable trials cannot be carried out because of resource constraints. The lack of a trial alone cannot be used as grounds for a PCT choosing to fund the treatment. For a commissioner to agree to fund a treatment solely for this reason would be perverse.

Commissioners have always differentiated between efficacy and clinical effectiveness although there is no agreed definition of these words in the commissioning context. Commissioners may find the following definitions of assistance.

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.

There are four main reasons why a treatment might be considered efficacious but not clinically effective.

1. The trial is poorly designed so that it cannot answer the question of interest. The lack of head to head studies is of particular concern. Some 'studies' are not strictly clinical trials at all – the most common being case series reports.
2. Use of invalid proxy outcome measures. A proxy outcome measure is a measure used as an alternative to the clinical outcome of interest. A classic example is the use of 'time to progression' in the study of cancer drugs and its use as a measure for increasing survival from cancer.

3. Inappropriate duration of the study, in which the follow-up time is too short to establish whether the long term clinical outcomes claimed are actually realised and whether others, that had not been predicted, do occur – this is particularly important in the context of patient safety.
4. Treatments often perform less well in practice than under trial conditions. The reasons for this include: clinical expertise/interest, patient selection, variable clinical practice, and loss of the Hawthorne effect (a placebo effect specific to trials). While it is not always possible to anticipate the likelihood of a discrepancy between trials and a routine NHS setting in advance, it is sometimes possible to anticipate the circumstances in which this might be a problem.

Licensing processes (such as drug licensing, the Medicines and Healthcare products Regulatory Agency approval for medical devices, and the National Institute for Health and Clinical Excellence's interventional procedures programme for invasive procedures) are designed to assess safety and efficacy. They do not address either effectiveness or cost-effectiveness.

It is also possible for a treatment to be clinically effective in theory but for this potential to be unrealisable. Evaluation of what *actually* happens once a treatment is released into the NHS is necessary in many areas of care but rarely happens. It is therefore possible that the NHS is paying for treatments which have been established for years without the NHS really knowing what good (or indeed harm) they are doing.

For many treatments only time and experience and/or proper formal evaluation can establish the *optimum use* of the treatment.

Experimental treatments

What is an experimental treatment?

The primary practical and legal duties of Primary Care Trusts are to aim to provide as comprehensive a healthcare service as possible (including the prevention of infection and illness) across all patient groups and across the entire patient pathway, and to stay within the financial budget allocated to them. Given that demand/need exceeds resources available, the funding of experimental treatments has to have a lower priority than funding treatments of proven benefit, providing basic services such as palliative care and improving service quality (particularly as it relates to national targets such as waiting times).

Suggested criteria for considering a treatment as experimental include: ^{1 2}

- The treatment is still undergoing clinical trials 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.

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<http://www.tac.vic.gov.au/jsp/content/NavigationController.do?areaID=26&tierID=2&navID=D9A78E597F0000100BCE28AD6298AC3&navLink=null&pageID=1328>

² <http://medical-dictionary.thefreedictionary.com/Experimental+treatment-criteria>

- 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.

A commissioner might also include the following two criteria:

- The evidence is as yet unavailable for public scrutiny.

The reason for adding this criterion lies in the fact that there is often a hiatus between the end of a clinical trial and the availability of evidence. Sometimes some evidence is either not made available or positively withheld. Given that there is a publication bias in favour of positive results, if a commissioner is aware that evidence is being withheld, it is proper to consider a treatment experimental until that evidence is publicly available for scrutiny.

- The PCT does not have confidence in the evidence base that has been presented.

Primary policy position of primary care trusts on experimental treatments

It is standard practice for PCTs not to fund treatments which are still considered experimental, irrespective of the 'potential' health benefit for either individuals or groups of patients.

The primary reason for adopting this policy is that it is difficult to justify funding an experimental treatment with outcomes which are either unproven or unclear when many proven interventions and important elements of healthcare remain either unfunded or are not fully accessed by sections of the population.

Exceptions to the general rule

On occasions, however, a PCT may wish to fund an experimental treatment. Before doing so, a PCT needs to reassure itself of three things:

1. That the decision to agree an exception is made for very clear and explicit reasons which are consistent with the PCT's overall priority setting principles.
2. That the PCT takes a policy position in relation to the specific treatment (i.e. decides whether it works, does not work, or remains experimental) and does not resort to patient-by-patient decision-making.
3. That funding experimental treatments is done in a way that will contribute to the knowledge base.

There are a number of common scenarios in which funding an experimental treatment might be considered.

Scenario 1: Experimental treatment for rare clinical situations and where the commissioner judges that trials will be impossible to carry out

PCTs often receive funding requests for experimental treatments supported by an argument that trials are impossible. It is recognised that there are circumstances where the potential for trials is restricted because of the nature of the treatment and/or the epidemiology of the disease. The case is, however, overstated. For example, there are tens of thousands of individuals suffering from Gaucher's Disease which is considered an ultra-orphan disease. Robust multicentre international trials, whilst a major challenge, are possible. Rarity is therefore not always sufficient ground for accepting lack of evidence. It is important for the PCT to distinguish between those instances where trials are either impossible or improbable and those where the research community and industry have not prioritised a trial.

Having ruled out those treatments where trials are possible, the PCT is then presented with a proposal for which there is either:

- no evidence, or
- only anecdotal evidence from very small case reports, or
- evidence of effect in a similar common condition that nevertheless does not translate completely to the proposal under consideration.

Here the commissioner has to approach the decision as though it were any other service development, albeit a 'service development for a single patient'. This is done by:

- judging the potential benefit and risks;
- assessing value for money; and
- prioritising the patient's need vis-à-vis other competing demands.

The main difference between this and normal service development assessment is that the judgment about benefit rests on biological plausibility of benefit by seeking a view on the biological mechanism and/or extrapolating information from unrelated cases.

If, after having considered the issue, the commissioner is minded to fund *and* can afford to do so – then there are three options open to the PCT:

1. Fund on the condition that the patient enters a properly conducted '*n of 1*' trial (including the adequate blinding of recipients, providers and assessment and having objective and relevant outcome measures). England does not currently have such a trial unit and so this option is not currently available.
2. Fund the treatment for a period of time and make ongoing treatment subject to demonstration of benefit for an individual patient using locally agreed criteria. Under these circumstances there should be agreement about the timescales of the trial, the measurable outcomes against which to determine

ongoing treatment). Such an approach is often *erroneously* referred to as an n of 1 trial. It is more appropriately called a *trial of treatment*.

3. Fund with no additional conditions. A report providing an update on the patient's progress should be requested from the clinician.

In all instances where a clinical database or a population registry operates, data should be submitted to this as a condition of funding.

Scenario 2: Experimental treatments that are currently being studied but require the PCT to sponsor individual patients to enter into a trial.

Most research is Industry-sponsored and so this situation does not commonly arise. However, PCTs do regularly fund excess service costs of non-Industry trials such as those conducted by the Medical Research Council. This funding arises out of the Concordat that exists between the Department of Health and research bodies. It is a memorandum of understanding and as such does not extend to directing PCTs to support such research. In reality PCTs are rarely aware of the fact that they are supporting a trial because additional hospital activity related to the trial is logged under routine contract activity such as a diagnostic or chemotherapy episode. It is only when the activity sits outside normal contracts that PCTs are asked to meet these costs and sometimes they will (legitimately) decline to do so.

There are some areas of clinical practice – most notably in the treatment of haematological and childhood cancers – where routine treatment is commonly delivered within the context of trials. As more clinical research networks are established within the NHS this practice will no doubt increase.

Only rarely is a commissioner explicitly asked to fund either excess service costs or the whole treatment. In these instances the following should be considered:

- The potential strategic importance of the treatment. This is essentially a judgment as to whether the trial will address the key goals and priorities of the programme area. The collective experience of commissioners suggests that opportunities of this kind are rare, as most funding requests for experimental treatments are for second, third and fourth line treatment for the seriously ill, as a last resort. Equally uncommon are requests to fund patients in trials which address specific questions for an existing and established treatment.
- The quality of the trial and whether or not it is going to generate the sort of information needed to come to a view on the treatment.
- Ownership of the data. Public funds should not be used to support trials where there is no guarantee that the full data will be put into the public domain.
- Whether the trial can be afforded and whether it should be prioritised over competing needs.

The most common situation in which PCTs find themselves is as the recipients of requests to fund ongoing treatment once the trial has ended. Generally PCTs do not fund trial pick up. Very occasionally funding is sought before a patient is entered into a trial. In these instances a patient's participation in the trial is dependent on the PCT picking up funding at the end of the trial. Here the assessment is the same.

Because these requests relate to Industry sponsored trials, bullet points 2 and 3 (immediate above) play a particularly important role in the assessment.

Scenario 3: Potentially important treatments which are of great interest to public authorities but not to other stakeholders.

Very rarely PCTs may consider an experimental treatment so important that they wish to see a publicly funded trial established. Given the lack of R&D and Industry support for these types of trials, it may be necessary to initiate and fund the trial themselves.

Treatments for which there are adequate trials and which have demonstrated effectiveness but for which concerns remain over the true value of the treatment.

It is not uncommon to have a situation where a treatment is supported by reasonably good trials but important questions still remain about the treatment. In these instances post licensing / trial evaluation is legitimate. Unfortunately, treatments, associated with high risks (eg: high budgetary impact, potential for clinical creep, uncertainties about risks and true benefits, etc.) are all too often released into the NHS without a *planned* review and without *planning* the assessment to inform that review. This is one area where the NHS needs to expand its formal evaluation of treatments.

Non-drug interventions often have a sparse evidence base and present a particular challenge to commissioners.

Issues that might result in a commissioner feeling that a treatment should only be made available if there is ongoing evaluation include but are not limited to:

- Where there are concerns about the true nature of the benefit and/or risks.
- Where a treatment's true place in management has yet to be established.
- Where there is potential for significant variation in clinical practice (which might otherwise be difficult to control).
- Where it is not known how best to deliver the treatment (e.g. dose, frequency, sequencing, concurrent treatment, duration of treatment).
- Where there is a good chance that real-life effects and/or costs may differ from those seen in clinical trials because of difference in context, patient mix, treatment delivery, service provision etc.

Those making funding decisions should, therefore, be able to apply conditions of funding which include access to a treatment through a trial or other form of clinical study. The National Institute for Health and Clinical Excellence is considering the use of an 'Only in Research' recommendation. The place of this category of recommendation and how such a recommendation is then translated into a trial is only now starting to be considered nationally, although commissioners have been using this as a policy option for years (although very rarely initiating and funding the trial themselves). A key difficulty has been that trials need clinicians who are

interested and willing to carry out the trial and a system for national or multicentre co-ordination as well as achieving consensus on research priorities amongst large numbers of PCTs. This option is not universally supported, but commissioners would argue that to release a treatment with unknown or high budgetary impacts whilst not knowing the true benefits and costs is indefensible. There is also debate about the research methodologies that could be informative enough in these circumstances; in particular there is debate about the potential of disease registers and audit to improve the evidence base for individual treatments.

Existing treatments

The NHS does not build in evaluation of treatments as they are introduced into the NHS. There are a number of treatments which are in current practice and routinely commissioned but whose benefits, and sometimes risks, should be better understood. This is particularly so for treatments whose use has expanded without any underpinning evidence (a phenomenon known as “clinical creep”).

There are times, therefore, when commissioners may wish to review an existing treatment.

Using research to address value for money and affordability issues

There are treatments which present a different set of problems. These are:

- Effective treatments which provide significant health benefits and which fall above the accepted cost-effectiveness threshold³.
- Effective treatments which fall below the threshold but whose budgetary impact is considered too high to be affordable (i.e. the opportunity costs are too great).

The question, in both the above instances, is “How does the NHS approach potentially useful treatments which are not cost-effective or not affordable although they are clinically-effective?”

Price negotiation is one option but this is not usually available to PCTs.

Another option is to explore ways of obtaining a similar outcome at much lower cost. This is particularly pertinent to the new biological drugs which are often licensed at a dose higher than that which is needed to deliver a clinical effect. PCTs should bear in mind that they do not owe a duty of care to patients and that, throughout the history of the NHS and in all other healthcare systems internationally, there are clinically effective treatments which are not provided to patients because they are deemed not to be cost effective or cannot be afforded. Thus research to provide more cost effective solutions for patients has a legitimate role.

³ Note there are three categories of treatments which fall above the threshold: those that are not cost-effective because they are poor treatments (such treatments need no further attention and should not be funded), those that are not-cost effective because of pricing but which provide valued health benefits in the opinion of the PCT and whose costs might be brought down to acceptable levels, and finally treatments which provide valued health benefits but which will always stay above the threshold (biological ultra-orphans being a case in point). Each has its own decision path and it is the second group which is referred to here.

Public value research

The above illustrates a number of instances where commissioners could fund research directly. Such research could be justified by a public body, as the return on the investment will accrue to society generally rather than the licence or patent holders of the technology under investigation.

However the greatest challenge for PCTs in funding such clinical trials is to secure the mandate for undertaking certain types of trials. Until there is wider support for public value research, options will always be limited and controversial.

Even with a mandate, the successful implementation of a more systematic approach to public value research requires a number of methodological and organisational issues to be given further consideration.

What is the best trial design needed to answer particular policy questions?

It is important that there is clarity about how best to answer specific policy questions. The application and limitations of cohort studies, registers, and other methodologies such as 'n of 1' trials need to be better understood. There is an increasing trend to use cohort studies and databases in a commissioning context but they have limitations which are not widely appreciated.

It is critical that if PCTs are to invest in trials they should invest in *sound research*. It is unacceptable to invest in evaluations and trials which have a poor design.

How might public value trials be best organised?

Getting trials of this nature off the ground requires a national and co-ordinated system of decision-making amongst the many different partners involved.

Because of the current political climate, there is sometimes only a short window of opportunity to initiate a trial. In these instances, the equivalent of an emergency planning team is needed. Existing R&D funding bodies cannot make decisions in a sufficiently timely way to meet some of the needs of PCTs. Alternative supporting structures are therefore needed.

The capacity of public bodies, including commissioners, to fund trials is limited and so any support structure would need to have a prioritisation process.

How might these trials be funded?

There are potentially a number of partners who could contribute to public value research.

Experience suggests that funding to providers has to be streamlined and the IVAN trial has established a unique framework for funding a trial from multiple sources. The IVAN trial is a head-to-head comparison of the efficacy and safety of Avastin and Lucentis for wet or neovascular age-related macular degeneration⁴.

⁴ For details see <http://www.ivan-trial.co.uk/>

In 1997 the Department of Health issued a series of documents which addressed NHS funding of service costs associated with non-commercial R&D. The most important of these is the Concordat, between the Department of Health in the UK and the Medical Research Council and other similar bodies, which sets out the obligations of the NHS routinely to fund the service costs related to non-commercial R&D. Guidance was issued to the NHS in HSG (97)32 (May 1997): *Responsibilities for meeting patient care costs associated with R&D in the NHS*. A more recent related document is *Attributing revenue costs of externally funded non-commercial research in the NHS (ARCO)* published in 2005.⁵ The division of service and treatment costs, as being something separate from research costs, is somewhat arbitrary. All costs of conducting a study are arguably correctly designated as research costs. However this probably reflects how funding has been traditionally structured in the UK.

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⁵http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4125280