British Society of Gastroenterology (BSG) Endoscopy Quality Improvement Programme (EQIP): Implementing new endoscopic techniques and technologies into clinical practice

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Abstract

Endoscopy has rapidly evolved from a diagnostic modality to a therapeutic tool with the advent of new technologies (medical devices or imaging) and techniques (types of procedures). Although the rapid advancement of technology is welcomed, this can pose its own problems if there is no robust system in place to assess the safety and efficacy of new endoscopic devices or practices or guide its use amongst clinicians prior to adoption. This is unlike the rigorous process medical drugs need to go through from pre-clinical to clinical phases of development, often with controlled trials being conducted prior to integration of a new drug into clinical practice. In this review we will identify the problems related to implementation of new technologies and techniques as well as propose solutions. We will outline the use of comparative effectiveness studies as a model for assessing new technologies and provide a structured pathway to support clinicians in their endeavour to introduce new devices or procedures in their clinical practice safely. We will also discuss the role of the British Society of Gastroenterology in risk stratifying new techniques and supporting clinicians in setting up national registries, training and business case development. This review will provide a framework for improving the quality and safety of our current practice of implementing new endoscopic technologies and techniques in the NHS.

Key points

- Endoscopy is rapidly evolving into a more complex therapeutic tool with the development of new technologies and techniques in this field
- However at present, new technologies and techniques are not subject to stringent evaluation of safety and efficacy prior to adoption
- Large scale randomised controlled trials may not always be feasible in endoscopy device/new technique research
- Comparative effectiveness (Phase II) studies should be explored as a model for research in new technologies in the NHS
- The British Society of Gastroenterology should play a leading role in risk stratifying new techniques, collaborating with NICE to support the evaluation of new devices and supporting clinicians with training and business case and tariff development

Background

The role of endoscopy has evolved over the last two decades from a diagnostic tool to an important therapeutic modality due to the development of a whole range of novel endoscopic techniques (procedures) and technologies (devices, including imaging). In this "white paper", we will discuss the problems and solutions identified to enable evidence based and safe adoption of both new techniques and technologies (see Table 1, Figure 1 & 2 for examples).

New Technologies

Unlike pharmaceutical regulation, device regulation differs substantially and is much less rigorous. Most devices get introduced into clinical practice without any comparative studies or randomised controlled trials (RCT). A device only requires CE marking, which until recently did not require any human data. As no strong clinical efficacy data is required before the device is used in patients, there has been no push from industry or clinicians to conduct comparative studies. Industry has traditionally spent money on marketing rather than research and evaluation of the device. This has resulted in the development of a range of devices and technologies which are still struggling to find a clear place in clinical practice.

New Techniques

Whilst the introduction of a new drug or device involves some form of regulation, there is no regulatory obligation pertaining to introduction of a new technique into daily clinical practice. The advantage of this is an easy introduction of low risk techniques into practice. However, the major disadvantage is that high risk techniques [e.g. endoscopic submucosal dissection (ESD) or per oral endoscopic myotomy (POEM)] could potentially be applied to patients without substantial evidence of its effectiveness or a credible measure of the endoscopist's competence. This could potentially cause harm to patients as highlighted by data from the French ESD experience where a high bleeding and perforation rate was encountered in the earlier phase of the study.[1]

Strategic Aims

- To develop a model whereby investigators, clinicians, patients, funders and industry strongly consider conducting comparative effectiveness studies during the development of a new technology
- To safeguard the best interests of patients exposed to new technologies or techniques
- To support clinicians in the rapid but safe introduction of new endoscopic technologies or techniques in daily clinical practice by providing a structured pathway
- To facilitate and inform National Institute of Health and Care Excellent (NICE) review of novel technologies and techniques
- To facilitate development of codes and tariffs for new technologies and techniques

Problem

Assessment of New Technologies

The traditional pharmacological model of pre-clinical and then clinical studies with safety and efficacy data followed by large regulatory multicentre Phase III RCTs (often at a cost of

several hundred million dollars), is problematic for devices and is not required from a regulatory perspective (Table 2). Device safety studies may be required, but can often be performed in a single centre with relatively small numbers of patients. In general device companies are smaller than pharmaceutical groups, and lack resources to deliver large scale multi-centre RCT. As device development is often incremental rather than leading to immediate practice change, a “blockbuster” product is less likely. Patent protection for devices is not as good as drugs and often competitors launch “copycat devices”. Profit margins for devices are smaller than in pharmaceuticals. This explains the urgency for launch soon after product development by the industry.

This has led to clinical data being developed as single “expert centre” case series, which are often single operator, may not be consecutive, and do not have comparators, let alone randomisation or blinding (i.e phase 0/I studies). The scientific value of such data for clinical decision making is exceptionally limited. This data and perceived expert endorsement is then used to support product marketing. This can lead to a peak of expectation as part of a “hype cycle” which is then dashed as more mature data emerges with subsequent disillusionment (Figure 3).[2]

Patients, clinicians and healthcare providers alike require robust data on safety and effectiveness of novel technologies. The recent scandal and public concerns on the safety of hernia mesh repair devices which have been in use for over 5 years now (with complication rates estimated now at between 12-30%) have highlighted the need for more rigorous evaluation of new devices.[3] Comparative safety and effectiveness data on devices should be available in order to enable the patient and clinician to choose between medical devices and understand potential complications. There is therefore a gap between the data offered by current regulatory and business models for device companies (phase 0/I) and the data end users would like (phase III/IV).

Assessment of New Techniques

New techniques are developed by individual clinicians with no commercial involvement. The burden of proving the value of new techniques therefore falls on clinicians rather than the industry and there is a danger that certain techniques can be carried out without evidence of safety and efficacy. Unlike drugs or devices that have been tested to establish the right method of use or dosing regimen that can be replicated easily, the outcome of a new technique is user dependent. The safety and effectiveness of the technique is dependent in many cases on the operator's training and skills which may not be formally accredited.

The existing model of pre-clinical followed by clinical studies and large multicentre randomised controlled trials to generate robust outcome data cannot be applied to assess new techniques primarily in view of the cost and resources this would entail. Unlike pharmaceuticals or devices, most new techniques are developed by clinicians innovating existing practice with no additional infrastructure, business or marketing platform. It is extremely challenging in this situation to progress to securing the financial investment required from industry or other future stakeholders in order to run a clinical trial to assess outcomes of the technique.

As with new technologies, a similar problem of limited clinical data generated from single centre, single operator case series has arisen. This data is of limited value as the results are often subject to positive reporting bias and does not take into account the user variability.

New techniques in particular carry an additional burden of training on top of the evidence base required. Technique related outcome is dependent on the training, skills and experience of the operator which therefore means it is essential to develop a framework which addresses these issues prior to the introduction of novel techniques into clinical practice.[4] This initiative and investment is less likely to come from the commercial sector, and therefore has to be driven by national societies like the BSG.

Initiatives and Solutions

New Technologies

On 26th May 2017, the CE marking process was changed and a new MDR (Medical Device Regulations) directive was issued[5]. The approval process now requires some evidence of efficacy (human data) and it is mandatory to have a post-marketing surveillance plan to collect and publish data.
This is a welcome change and will drive more product evaluation before and after launch but will still not result in a well designed multi-centre RCT before product launch.
Costs for robust clinical trials are significant, especially if a Clinical Research Organisation (CRO) is involved. There is a risk that the product will not be better, or at least not significantly better than the comparator. Effect sizes in studies tend to decease as the quality or phase of trials increase[6]. Therefore, to change this dynamic, research must be relatively low cost, relatively low risk, and offer some commercial benefit.

Phase II trials in the NHS offer a potential model, where by multi-centre, multi operator data with a comparator to demonstrate safety and efficacy would satisfy many of the concerns clinicians, healthcare providers and patients have. Such trials are smaller scale than phase III trials, and a less rigorous test of a product, but may be less prone to rejecting a product due to a type II error. Phase II data is much more likely to be favourably viewed by quasi-regulatory agencies or financial gatekeepers e.g. NICE or clinical commissioning groups (CCG), compared to Phase 0/I. They also potentially smooth the hype cycle curve (Figure 3), helping long term adoption of new technology.

In order to reduce costs but maintain study quality three elements might be combined (Figure 4):

- Industry support, both limited financial and free devices
- NIHR portfolio research infrastructure
- Inclusion of clinical trials units in design and execution of studies

A recent example of this was the BSG supported ADENOMA study that delivered a 1700 patient multi-centre randomised controlled trial for an industry cost of approximately £150,000 plus free devices.[7] The use of the Endocuff Vision device in this study was shown to significantly improve adenoma detection rates which has implications for a change in

conventional practice. In comparison to pharmaceutical type phase III CRO delivered studies this represents exceptionally good value.

In order to incentivise the low-cost research strategy above, there needs to be a commercial pay-off for the research investment. This might come in endorsement from NICE e.g. HALO in Barrett's[8], BSG or other partner organisations, or clinical commissioning groups. The latter recently have begun to use "lavender statements" where treatment or devices without robust evidence, or not supported by invasive procedures assessment by NICE[9], are excluded from funded clinical options available to clinicians. Such groups of healthcare payers might rank or differentially support the use of devices dependent on their evidence base.

New Techniques

Given the paucity of regulation surrounding the adoption of new endoscopic techniques, we propose that all new techniques are subject to review by the BSG and risk stratified. Development and dissemination of information related to new techniques should be channelled via regular literature review, position statements and the use of online tools (e.g. a novel techniques and technologies section on the BSG website). Easy access to validated, well researched information on a new technique can also be used by future adopters to produce patient information sheets.

In order to guide the implementation of a new technique in the NHS, clinical pathways should be developed and service delivery standards (key performance indicators/KPI) defined - in a similar style to what has been advocated for diagnostic endoscopy.[10] NICE initiatives such as the Medical Technology Evaluation Programme (MTEP) and the Interventional Procedures Programme (IPP) were set up to identify and select appropriate medical technologies and techniques for evaluation and to generate recommendations for use or develop guidance. Notifications of new technologies are made to NICE primarily from product manufacturers and are evaluated nationally if they meet selection criteria. One drawback of this approach is that there may be a selection bias in the technologies proposed for evaluation as not all manufacturers (e.g non UK based) are aware of this NICE initiative. We recommend that the BSG adopts a leading role in notifying NICE of new techniques/technologies and supports the evaluation process by gathering evidence and providing experts. This method of collaborative working between the BSG and NICE using existing committees and frameworks will allow for a more streamlined approach to evaluation and publication of guidance on techniques and technologies that benefit both the patient and healthcare system.

Registries, training and business cases

As outlined in the previous section, randomised controlled clinical trials comparing a new technique with the current standard are not always feasible to conduct. However, setting up a national clinical registry on a particular new technique provides a structured mechanism for its introduction and enables data collection on safety and effectiveness outcomes across multiple sites and users. This is also useful even once a technique is adopted by NICE when regular audit is required. Registry data can also be used to identify core research questions

and provide pilot material to inform the design of a comparative effectiveness study. We foresee that funding of these studies based on research priorities can be derived from the NIHR portfolio research infrastructure and industry grants. A BSG supported National ESD registry best exemplifies this[11]. This was supported by a small grant from multiple industry partners and adoption by NIHR.

In view of the fact that operator skill and experience are a significant factor in the success of a new endoscopic technique, it is imperative that a technique/procedure specific training framework is developed in order to deliver high quality, standardised training. This should involve both theoretical knowledge acquisition (potentially deliverable through a web-based training platform) and step wise hands on training (including the use of animal models where applicable). The BSG is in a good position to identify suitable training centres and experts for mentorship. In order to fund this training, the potential for commercial partnership grants with relevant industry partners should be explored. A formal accreditation process into novel techniques should also be thought through.

In the current NHS climate, there can sometimes be little incentive for a clinician to adopt a new technique despite its effectiveness due to the considerable time and effort required to draft a business case that would justify its introduction. The BSG should aim to provide a hub with support for business case development in specific selected new techniques backed by an evidence base. It should also facilitate the development of new codes and tariffs enabling appropriate remuneration from the payer (clinical commissioning groups). These tariffs will be the key to success of a business case in each individual NHS trust or hospital.

Conclusion

Rapid advances in novel endoscopic technologies and techniques provides a unique opportunity for our patients to have earlier neoplasia detection and minimally invasive endoscopic therapy instead of traditional radical surgery with its associated morbidity and mortality. In the absence of a legal regulatory framework for introduction of new techniques, this BSG initiative would develop a safe platform for introduction of these novel techniques into clinical practice.

Phase II comparative trials offer a “bridge” between the competing desires for excellent clinical evidence, and the regulatory and financial pressures that device manufacturers face. The UK and BSG are well placed to engage with industry to offer low cost, high quality innovative research models, and to support the outcomes of such research, with support for subsequent differential usage of evidence based products to encourage commercial engagement.

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Potential Conflicts of Interest

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PB: Consultant for: Aquilant, Fujifilm, Olympus, Pentax, Boston Scientific, 3D Matrix, Interscope, Norgine

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PB - devised idea for the manuscript, drafted content on new techniques and provided critical final revision of the article
SS - researched content for manuscript sections, drafted content on new techniques and revised manuscript
JEE - devised idea for the manuscript, drafted content on new technologies and provided critical final revision of the article

Table 1: Examples of New Technologies and Techniques

Technologies	Techniques
Full thickness resection device (FTRD)	Endoscopic submucosal dissection (ESD)
Cryoablation balloon	String traction at ESD (TAC)
Endocuff Vision®/EndoRings™	Submucosal tunnelling endoscopic resection (STER)
Confocal laser endomicroscopy	Knife assisted snare resection (KAR)
Volumetric laser endomicroscopy	Per Oral Myotomy (POEM) or G-POEM
Colon capsule	Underwater endoscopic mucosal resection
Topical haemostats (e.g. Hemospray®, EndoClot®, Purastat®)	Direct cholangioscopy
Full Spectrum Endoscopy (FUSE)	EUS-radiofrequency ablation
Endocytoscopy	EUS-biliary drainage
Artificial intelligence and machine learning (polyp detection and characterisation)	EUS guided endoscopic gastrointestinal anastomosis
Submucosal lifting solutions e.g. Eleview®	Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST)
Stretta device for gastro-oesophageal reflux	Duodenal mucosal resurfacing
OverStitch™ endoscopic suturing system	Endoscopic sleeve gastrectomy

Table 2: Traditional Pharmacological Model of Trials

Phase 0	Phase I	Phase II	Phase III	Phase IV
Pre-clinical models e.g. Animal cadaveric	1st in Human, safety and development (single centre) N=10-50	Multi-operator, Multi-centre (few) Safety and efficacy N=100-200	Definitive community based trials N=500-1000 (Networks)	Post-marketing surveillance N=100-1000s

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