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Welsh Health Specialised Services Committee (WHSSC)

Title: Introduction of New Technologies into NHS Wales – Perspective of the Welsh Health Specialised Services Committee

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EXECUTIVE SUMMARY

This paper is directed towards NHS Wales being able to identify, assess and implement new technologies within a robust, effective, efficient and timely framework. The focus of this paper is an integrated and collaborative approach centred on a Heath Technologies Assessment process involving patients, clinicians, manufacturers and commissioners. It describes 2 different systems for designating and appraising new technologies (Fast Track and Breakthrough) likely to be of significant benefit to NHS Wales, designating priority review coupled with a rapid implementation and outcomes assessment framework. The work draws from a number of systems around the world including the Food and Drug Administration (FDA), Australia, New Zealand, NICE and a number of different European States.

The establishment of such an All Wales Agency is vital to ensure that the processes and procedures outlined in this paper are conducted efficiently and effectively and a collaborative approach is established to ensure a consistent approach across Wales for the following objectives:

- Early interactions with manufacturing sponsors on promising new technologies (including involvement in study design and potential study centres in NHS Wales);
- Expedited evidence programmes;
- Expedited implementation programmes;
- Outcomes and monitoring;
- A collaborative strategic approach that brings together the perspective of all stakeholders;
- Aimed at improving healthcare delivery (acceptability, accessibility, appropriateness, effectiveness, efficiency, safety);
- Ensure collaboration and joint decision-making;
- Promote the use/uptake of research evidence;
- Share best practices across the province;
- Share knowledge, clinical experience and learning to reduce variation and improve care;
- Work together to develop new and innovative approach to care

The paper describes key concepts and processes in prioritising which new technologies should be forwarded for expedited assessment, who should undertake these assessments, how new technologies could be implemented into NHS Wales at low clinical and organisational risk and how the outcome measures should be described, assessed and used for commissioning.

This is a much more expanded role than that currently provided by either AWMSG, NICE or the SMC in the UK which are primarily concerned with the Health Technology Assessment process itself. The paper describes an expanded role for an All Wales Agency (referred to as the 'The Agency' in this document) who purpose should be to co-ordinate the processes outlined in this paper and oversee the Health Technology Assessments undertaken and the wider collaborative processes required to implement recommendations efficiently. This would require a new way of working and not merely expanding an existing body like AWMSG.

I INTRODUCTION

On the 17 February 2014, the Welsh Health Specialised Services Committee (WHSSC) were asked to provide oral evidence following a written submission to the Health and Social Services Select Committee on the introduction of new technologies into NHS Wales.

As and output from the meeting, the representatives from WHSSC were asked to provide formal written submissions on how this could be achieved by the Chair of the Committee, Mr David Rees.

This paper represents the thoughts of how this could be achieved in NHS Wales. The focus of this paper is an integrated and collaborative approach centred on a Heath Technologies Body involving patients, clinicians, manufacturers and commissioners; 2 different systems for identifying and appraising new technologies (Fast Track and Breakthrough) likely to be of significant benefit to NHS Wales, Priority Review and rapid implementation and outcomes assessment. The work draws from a number of systems around the world including the Food and Drug Administration (FDA), Australia, New Zealand, NICE and a number of different European States.

II SCOPE

This paper is focused on new technologies that are intended for use for the treatment of serious health conditions. Wider facilitative technologies (e.g. IT, communications etc) are outside the scope of this paper.

The scope includes:

- Early interactions with manufacturing sponsors on promising new technologies (including involvement in study design and potential study centres in NHS Wales);
- Expedited evidence programmes;
- Expedited implementation programmes;
- Outcomes and monitoring;
- A collaborative strategic approach that brings together the perspective of all stakeholders;

- Aimed at improving healthcare delivery (acceptability, accessability, appropriateness, effectiveness, efficiency, safety);
- Ensure collaboration and joint decision-making
- Promote the use/uptake of research evidence
- Share best practices across the province
- Share knowledge, clinical experience and learning to reduce variation and improve care
- Be involved in planning for health-care service delivery
- Work together to develop new and innovative approach to care

III BACKGROUND: SUMMARY OF THE EXISTING REGULATORY FRAMEWORK FOR MEDICINAL DRUGS AND DEVICES

1. Regulation of Pharmacotherapeutics

In order to be able to market a drug or device in Europe, certain legislative and regulatory processes must be adhered to before marketing authorisation is permitted. The European Medicines Agency (EMA) is a decentralised agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. It began operating in 1995.

Under the centralised procedure, pharmaceutical companies submit a single marketing-authorisation application to the EMA. Once granted by the European Commission, a centralised marketing authorisation is valid in all European Union (EU) Member States, as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway. By law, a company can only start to market a medicine once it has received a marketing authorisation.

Most of the EMA's scientific evaluation work is carried out by its scientific committees, which are made up of members from EEA countries, as well as representatives of patient, consumer and healthcare-professional organisations. These committees have various tasks related to the development, assessment and supervision of medicines in the EU, including Wales.

The EMA is responsible for coordinating the EU's safety-monitoring or 'pharmacovigilance' system for medicines. It constantly monitors the safety of medicines through the EU network and can take action if information indicates that the benefit-risk balance of a medicine has changed since it was authorised.

The EMA has a Pharmacovigilance Risk Assessment Committee (PRAC), which provides recommendations on the safety of human medicines. The Committee

for Medicinal Products for Veterinary Use (CVMP) and its Pharmacovigilance Working Party deal with safety issues for veterinary medicines.

It also supports methodological research, managing the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). This network aims to strengthen the monitoring of authorised medicines in Europe by facilitating the conduct of multicentre, independent, post-authorisation studies focusing on safety and on the balance of benefits and risks.

The EMA plays a role in stimulating innovation and research in the pharmaceutical and New Technologies sector:

- it gives scientific advice to companies on the development of new medicines;
- it publishes guidelines on the requirements for the quality, safety and efficacy testing of medicines;
- it provides special assistance to micro, small and medium-sized enterprises (SMEs) through its SME office;
- it issues opinions on orphan designation for medicines for rare diseases;
- it manages the Innovation Task Force, a group that provides a forum for early dialogue with applicants

The Agency is involved in the scientific evaluation of medicines that fall within the scope of the centralised authorisation procedure. However, thousands of other medicines that do not fall within this scope are marketed in the EU in individual EU Member States in accordance with national authorisation procedures not involving the EMA, or in several Member States through the decentralised or mutual recognition procedures.

The mutual recognition and decentralised procedures are overseen by two coordination groups representing the EU Member States: the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary (CMDv).

The Agency can become involved in assessing nationally authorised medicines if they are referred to the EMA through a referral procedure. This may be due to a safety concern or an issue that requires resolution in the interest of protecting public health. Significant emerging safety issues concerning a medicine marketed in the EU can be referred to the Agency under the urgent Union procedure regardless of the medicine's initial authorisation route.

2. Regulation of Medical Devices

The medical device and the *in vitro* diagnostic medical devices sectors are estimated to comprise more than 500,000 products, covering a wide range of devices from simple bandages to the most sophisticated life-supporting devices. Medical devices and in vitro diagnostic medical devices play a crucial and complementary role in the diagnosis, prevention monitoring and treatment of diseases, the safety of the blood used in transfusions, and the improvement of the quality of life of people suffering from disabilities. The medical device and in vitro diagnostic medical device sectors are characterised by a high degree of innovation, both incremental — once a device reaches the market, improvements may follow within 18 to 24 months — and breakthrough innovation.

The European Union has solid assets in the medical device and in vitro diagnostic medical devices fields and, without doubt, considerable potential to deliver growth. Not only the European Union has the largest market and some of the biggest companies in the world, but it also has an expanding ecosystem of innovative small to medium-sized enterprises, and even micro enterprises, which are the innovators of the future. The medical device and in vitro diagnostic medical devices sectors have already proven to be key drivers of European economic growth. They contribute substantially to European Union's balance of trade, employs more than 500,000 people in about 25,000 companies, 80 % of medical devices companies and 95% of in vitro diagnostic medical devices companies being small to medium-sized or micro enterprises. In 2009, they generated annual sales of around EUR 95 billion (EUR 85 billion for medical devices and EUR 10 billion for in vitro diagnostic medical devices) in the European (EU/EFTA) market11, the main markets being Germany (EUR 21 billion for medical devices and EUR 2.17 billion for in vitro diagnostic medical devices), France (EUR 17 billion for medical devices and EUR 1.7 billion for in vitro diagnostic medical devices) and the United-Kingdom (EUR 11 billion for medical devices and EUR 0.7 billion for in vitro diagnostic medical devices). Last but not least, they are sectors that invest heavily in research and development, as about 6-8 % of medical devices annual sales and 10% of in vitro diagnostic medical devices annual sales are ploughed back into research each year, equivalent respectively to some EUR 6.5 billion and some EUR 1 billion, usually through collaboration with healthcare professionals and academia, in order to better identify and respond to emerging medical needs.

Innovation in medical devices and in vitro diagnostic medical devices has gained pace in recent years. Scientific and technological progress, such as progress in drug-device combination products, tissue engineering, information and communication technologies (ICT), nano-science, personalised medicine and genetics, are creating new opportunities for improving healthcare and could culminate in a revolution in how healthcare services are delivered.

This innovation is central to the promotion of the smart, sustainable and inclusive growth which the European Union is determined to achieve through the Europe 2020 Strategy.

Safe and innovative devices have the potential to:

• keep people healthy and active for longer, by, for example, offering solutions for disease prevention or early diagnosis; this has a positive impact on productivity and competitiveness;

• make the healthcare sector more sustainable, as they can, for instance, help in preventing or reducing hospitalisation;

• improve skills and create jobs, since the healthcare sector employs one in ten of the most qualified workers in the European Union. With the proposed legislation, the Commission aims also at maintaining the competitiveness and innovation capacities of the medical device industry by further harmonising the rules governing the medical device and the in vitro diagnostic medical device sectors and the enforcement practices in the Member States. In particular, it is estimated that the establishment of a central registration tool would help reducing the administrative costs by up to EUR 157mio. Also an EU vigilance portal with central reporting of serious incidents instead of multiple reporting is expected to bring about non negligible reductions in administrative costs.

Progress in medical devices, in in vitro diagnostic medical devices and in information and communication technology (ICT) made it possible to radically transform the way healthcare services are delivered and to identify potential solutions to the demographic, societal and scientific challenges the European Union is facing.

In particular, over the last few years, e-Health technologies — many of which are medical devices or in vitro diagnostic medical devices — have created new possibilities for remote diagnosis, monitoring or treating patients and reducing hospitalisation, thus saving time and money for patients, healthcare providers and social security systems. Such innovations may offer the chance to make healthcare systems more efficient, thus providing equitable access to healthcare for millions of European citizens. These objectives are critical given the increasing incidence of chronic diseases, an ageing population and a shrinking healthcare workforce. E-Health provides important opportunities to improve overall healthcare delivery. However, to reap these benefits, e-Health still presents challenges that the European Union is determined to tackle through, in particular, the Digital Agenda for Europe, the e-Health Action Plan13 and the Directive on the application of patients' rights in cross-border healthcare14. This is necessary to achieve interoperable e-Health services in the European Union, to the benefit of patients (e.g. safety of treatments received and delivery of care at the point of need), healthcare professionals (e.g. improved quality and safety of

care and up-to-date patient status information) and industry (e.g. opening up competition, reducing development costs).

Globally, medical devices and in vitro diagnostic medical devices represented less than 5% of Member States' healthcare spending in 2011 (e.g. 3% in Germany, 4% in the United- Kingdom, 5% in Sweden)16, and offer alternatives to systematic or long-term hospitalisation, such as early diagnostic, minimally invasive surgical devices or home-use devices. In doing so so, medical devices support the long-term sustainability and efficiency of healthcare systems and have a positive impact on the productivity and competitiveness of the European Union's economy.

Medical devices and in vitro diagnostic medical devices are often an integral part of modern hospital services, and the strong link between a device and the surrounding environment often makes it difficult to correctly measure the added value of introducing an innovative device. The European Union supports projects aimed at improving health technology assessment methodologies for devices through the Seventh Framework Programme of the European Community for research, technological development and demonstration activities17. Improved methodologies will make it easier for health decision-makers to identify which new devices can contribute to efficiency gains and improved services. The establishment of a voluntary European Health Technology Assessment (HTA) network in 2013 will additionally enable easier sharing of HTA knowledge concerning devices and other health technologies among Member States.

The current EU regulatory framework for medical devices, other than in vitro diagnostic medical devices, consists of Council Directive 90/385/EEC on active implantable medical devices (AIMDD) and Council Directive 93/42/EEC on medical devices (MDD) which cover a huge spectrum of products. The MDD divides them into four classes of risk: class I (low risk, e.g. sticking plasters, corrective glasses), class IIa (medium-low risk, e.g. tracheal tubes, dental filling material), class IIb (medium-high risk, e.g. X-ray machines, bone plates and screws) and class III (high risk, e.g. heart valves, total hip replacements, breast implants). Active implantable medical devices (e.g. pacemakers, implantable defibrillators) covered by the AIMDD fall de facto into class III.

The two Directives, adopted in the 1990s, are based on the 'New Approach' and aim to ensure the smooth functioning of the internal market and a high level of protection of human health and safety. Medical devices are not subject to any pre-market authorisation by a regulatory authority but to a conformity assessment which, for medium and high risk devices, involves an independent third party, known as 'notified body'. Notified bodies, of which there are around 80 across Europe, are designated and monitored by the Member States and act under the control of the national authorities. Once certified, devices bear the CE

marking which allows them to circulate freely in the EU/EFTA countries and Turkey.

The existing regulatory framework has demonstrated its merits but has also come under harsh criticism, in particular after the French health authorities found that a French manufacturer (Poly Implant Prothèse, PIP) had for several years apparently used industrial silicone instead of medical grade silicone for the manufacture of breast implants contrary to the approval issued by the notified body, causing harm to thousands of women around the world. In an internal market with 32 participating countries and subject to constant technological and scientific progress, substantial divergences in the interpretation and application of the rules have emerged, thus undermining the main objectives of the Directives, i.e. the safety of medical devices and their free movement within the internal market. Moreover, regulatory gaps or uncertainties exist with regard to certain products (e.g. products manufactured utilising non-viable human tissues or cells; implantable or other invasive products for cosmetic purposes).

This revision aims to overcome these flaws and gaps and to further strengthen patient safety. A robust, transparent and sustainable regulatory framework should be put in place that is 'fit for purpose'. This framework should be supportive of innovation and the competitiveness of the medical device industry and should allow rapid and cost-efficient market access for innovative medical devices, to the benefit of patients and healthcare professionals.

This proposal is adopted alongside a proposal for a Regulation on in vitro diagnostic medical devices (IVDs), such as blood tests, which are covered by Directive 98/79/EC of the European Parliament and of the Council (IVDD). The horizontal aspects that are common to both sectors are aligned whilst the specific features of each sector require separate legal acts.

The regulatory instrument of 'common technical specification' (CTS), which has proven useful in the context of the IVDD, has been introduced in the broader field of medical devices to allow the Commission to further specify the general safety and performance requirements (laid down in Annex I of the EU regulatory framework) and the requirements on clinical evaluation and post-market clinical follow-up (laid down in Annex XIII of the EU regulatory framework). Such requirements however, leave manufacturers the possibility of adopting other solutions that ensure at least an equivalent level of safety and performance. The legal obligations on manufacturers are proportionate to the risk class of the devices they produce. For example, this means that even though all manufacturers should have a quality management system (QMS) in place to ensure that their products consistently meet the regulatory requirements, the QMS-related responsibilities are stricter for manufacturers of high risk devices than for manufacturers of low risk devices. Manufacturers of medical devices for an individual patient, so called 'custom-made devices', must ensure that their

devices are safe and perform as intended, but their regulatory burden remains low. Key documents for the manufacturer to demonstrate compliance with the legal requirements are the technical documentation and the EU declaration of conformity to be drawn up in respect of devices placed on the market. Their minimum contents are laid down in Annexes II and III of the EU regulatory framework.

The following concepts are also new in the field of medical devices:

•A requirement has been introduced that within the manufacturer's organisation a 'qualified person' should be responsible for regulatory compliance. Similar requirements exist in EU legislation on medicinal products and in the national laws transposing the AIMDD/MDD in some Member States.

•Since in the case of 'parallel trade' with medical devices application of the principle of free movement of goods varies considerably from one Member State to another and, in many cases, de facto prohibits this practice, clear conditions are set for enterprises involved in relabelling and/or repackaging medical devices.

•Patients who are implanted with a device should be given essential information on the implanted device allowing it to be identified and containing any necessary warnings or precautions to be taken, for example indication as to whether or not it is compatible with certain diagnostic devices or with scanners used for security controls.

•In accordance with Article 12a of the MDD, introduced by Directive 2007/47/EC, the Commission had to prepare a report on the reprocessing of medical devices and submit, where appropriate, a legislative proposal on this issue. On the basis of the Commission's findings set out in its report of 27 August 201016, which took into account the opinion of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) of 15 April 2010, the proposal contains strict rules on the reprocessing of single-use devices in order to ensure a high level of protection of health and safety whilst allowing this practice to further develop under clear conditions. Reprocessing of single-use devices is considered as manufacture of new devices so that the re-processors must satisfy the obligations incumbent on manufacturers. The reprocessing of single-use devices for critical use (e.g. devices for surgically invasive procedures) should, as a general rule, be prohibited. Since certain Member States may have particular concerns in terms of safety regarding the reprocessing of single-use devices, they retain their right to maintain or impose a general ban on this practice including the transfer of single-use devices to another Member State or to a third country with a view to their reprocessing and on the access of reprocessed single-use devices to their market.

The main shortcomings of the current system is its lack of transparency. Recommendations to rectify this as proposed by the EU consists of:

•A requirement that economic operators must be able to identify who supplied them and to whom they have supplied medical devices;

•A requirement that manufacturers fit their devices with a Unique Device Identification (UDI) which allows traceability. The UDI system will be implemented gradually and proportionate to the risk class of the devices;

•A requirement that manufacturers/authorised representatives and importers must register themselves and the devices they place on the EU market in a central European database;

•an obligation for manufacturers of high-risk devices to make publicly available a summary of safety and performance with key elements of the supporting clinical data;

•and the further development of the European databank on medical devices (Eudamed), set up by Commission Decision 2010/227/EU17, which will contain integrated electronic systems on a European UDI, on registration of devices, relevant economic operators and certificates issued by notified bodies, on clinical investigations, on vigilance and on market surveillance. A large part of the information in Eudamed will become publicly available in accordance with the provisions regarding each electronic system.

The establishment of a central registration database will not only provide a high level of transparency but also do away with diverging national registration requirements which have emerged over recent years and which have significantly increased compliance costs for economic operators. It will therefore also contribute to reducing the administrative burden on manufacturers.

2.1 Article 4 - REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009

Placing on the market and putting into service

- A device may be placed on the market or put into service only if it complies with this Regulation when duly supplied and properly installed, maintained and used in accordance with its intended purpose.
- A device shall meet the general safety and performance requirements which apply to it, taking into account its intended purpose. General safety and performance requirements are set out in Annex I.
- Demonstration of conformity with the general safety and performance requirements shall include a clinical evaluation in accordance with Article

49 of REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009.

- Devices that are manufactured and used within a single health institution shall be considered as being put into service. The provisions regarding CE marking referred to in Article 18 and the obligations laid down in Articles 23 to 27 shall not apply to devices, provided that manufacture and use of those devices occur under the health institution's single quality management system.

- The Commission shall be empowered to adopt delegated acts in accordance with Article 89 amending or supplementing, in the light of technical progress and considering the intended users or patients, the general safety and performance requirements set out in Annex I, including the information supplied by the manufacturer.

IV KEY OBJECTIVES

It is not the purpose of the following to substitute the proscribed **regulatory** processes (summarised in SECTION III) that are currently in place via European legislation for the regulation of drugs and medical devices.

However, the following does describes a framework and key processes that could allow for the identification, assessment, implementation and outcomes monitoring for the introduction of new technologies into NHS Wales. Any process targeted towards appropriate, robust and timely assessment and implementation must be based on a prioritisation process based on key regulatory principles implemented by an Agency resourced to be able to:

- Prioritise key new technologies, assessed to have a significant beneficial impact on the population of Wales;

- An ability to implement 'Fast Track', 'Break Through' and 'Priority Review' processes;

- An ability to work with key clinical groups to develop clinical access policies, service specification and quality and outcomes frameworks

These functions are not currently provided by any existing Agency in Wales but are established by other international authorities (e.g. USA, Australia, New Zealand). The establishment of such an Agency for Wales would also have the additional benefits of:

- Earlier involvement with the manufacturing industry in the design and involvement with clinical research;

- A more seamless and timely integration of evidence evaluation, clinical regulation, implementation, quality and outcomes assessment, procurement and re-evaluation

The following five programs are proposed to facilitate and expedite development, review, implementation and monitoring of new technologies to address unmet medical need in the treatment of a serious or life- threatening conditions: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation, implementation, outcomes monitoring (see Section IV for an overview of the programs). This paper provides a single resource for information on these potential policies and procedures for these six programs as well as threshold criteria generally applicable to conclude that a new technology is a candidate for these expedited development and review programs.

The programs described in this paper are intended to help ensure that new technologies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks. This thinking is similar that that prosed by other organisations[1].

V KEY CONCEPTS FOR EXPEDITED PROGRAMS

The programs that are the subject of this guidance, fast track designation, breakthrough therapy designation, accelerated approval, and priority review, are described in more detail below. As referenced above, the criteria for all three of these expedited programs draw on the same principle of addressing unmet medical need in the treatment of a serious condition, which is discussed below.

A. Serious Condition

Whether a Condition Is Serious

This document generally intends to interpret the term "serious" consistent with other authorisites (e.g. FDA, etc) for the purposes of accelerated approval, fast track designation, and expanded access to investigational technologies for treatment use. A serious disease or condition may be defined as:

"a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or

[1] e.g. the FDA first formally articulated its thinking on expediting the availability of promising new therapies in regulations codified at 21 CFR part 312, subpart E.5. The subpart E regulations were intended to speed the availability of new therapies to patients with serious conditions, especially when there are no satisfactory alternative therapies, while preserving appropriate standards for safety and effectiveness. The existing FDA regulations call for earlier attention to new technologies that have promise in treating such conditions, including early consultation with the Agency for sponsors of such products, and efficient trial design, potentially relying on well-controlled Phase 2 studies for evidence of effectiveness. The subpart E 46 regulations specifically recognize that patients and physicians are generally willing to accept greater risk (and uncertainty about benefit) for a treatment for a serious condition where there is an unmet medical need).

recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition[2] to a more serious one."

Whether the New Technology Is Intended to Treat a Serious Condition

As referenced in Section IV, as a general matter, the eligibility criteria for expedited programs require that a drug be intended to treat a serious condition[3]. To satisfy this criterion, a new technology must be intended to have an effect on a serious aspect of a condition, such as a direct effect on a serious manifestation or symptom of a condition, or other intended effects, including:

•A diagnostic product intended to improve diagnosis or detection of a serious condition in a way that would lead to improved outcomes;

•A product intended to improve or prevent a serious treatment-related side effect[4];

•A product intended to avoid a serious adverse effect associated with available therapy for a serious condition[5].

B. Available Therapy

This paper generally considers available therapy (and the terms existing treatment and existing therapy) as a therapy that:

•Is approved or licensed in Europe for the same indication[6] being considered for the new technology and;

[2] For the purposes of this guidance, this report considers the term condition to include a disease or illness. All conditions meeting the definition of life-threatening as set forth at by the FDA in 21 CFR 312.81(a) would also be serious conditions.

[3] In the US this comes under FDA regulation supported by appropriate legislation.

[4] e.g. serious infections in patients receiving immunosuppressive therapy

[5] e.g. significantly less cardiotoxicity than available cancer therapy

[6] Only in rare cases will a treatment that is not approved for the indicated use or is not European-regulated (e.g., surgery) be considered available therapy. In those cases, a relevant body may consider an unapproved or unlicensed therapy to constitute "available therapy" if the safety and effectiveness of the use is supported by compelling evidence, including evidence in the published literature (e.g., certain established oncologic treatments).

•Is relevant to current U.K. standard of care (SOC) for the indication being considered.

U.K. Standards of Care (SOC)

There may be a substantial number of approved therapies with varying relevance to how a serious disease is currently treated in the UK, including therapies that are no longer used or are used rarely. In the US, the FDA's available therapy determination generally focuses only on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed.

In evaluating the current SOC, consideration should be given to recommendations by authoritative scientific bodies (e.g., NICE, FDA, SMC) based on clinical evidence and other reliable information that reflects current clinical practice. In the absence of a well- established and documented SOC, Wales may consult with UK or other international experts for advice in assessing whether an approved therapy is relevant to the current SOC. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic or proteomic marker), the SOC for the broader population, if there is one, generally is considered available therapy for the subset.

Over the course of new technologies development, it is foreseeable that the SOC for a given condition may evolve (e.g., because of approval of a new therapy or new information about available therapies). The proposed Agency will determine what constitutes available therapy at the time of the relevant regulatory decision for each expedited program the sponsor intends to use[7].

A new technology granted accelerated approval based on a surrogate or clinical endpoint and for which clinical benefit has not been verified is not considered available therapy.

A new technology approved under accelerated approval with restricted distribution and a drug approved with a risk evaluation and mitigation strategy (REMS) that includes elements to assure safe use (ETASU) be considered available therapy only if the study population for the new technology would be eligible to receive the approved drug under the restricted distribution program or ETASU REMS.

C. Unmet Medical Need

[7] e.g. generally early in development for fast track and breakthrough therapy designations, at time of biologics license application (BLA) or new drug application (NDA) submissions for priority review designation, during BLA or NDA review for accelerated approval

An unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e. to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).

Where There Is No Available Therapy

If no therapy exists for a serious condition, there is clearly an unmet medical need.

When available therapy exists for a condition, a new treatment generally would be considered to address an unmet medical need if the treatment:

•Has an effect on a serious outcome of the condition that is not known to be influenced by available therapy[8];

•Has an improved effect on a serious outcome(s) of the condition compared to available therapy[9];

•Has a benefit for patients who are unable to tolerate available therapy or whose disease has failed to respond to available therapy, or the treatment can be used effectively with other critical agents that cannot be combined with available therapy;

•Provides efficacy similar to those of available therapy, while (1) avoiding serious toxicity that occurs with available therapy, (2) avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious condition, or (3) reducing the potential for harmful drug interactions;

•Provides similar safety and efficacy as available therapy but with another documented benefit, such as improved compliance, that is expected to lead to an improvement in serious outcomes;

•Addresses an emerging or anticipated public health need, such as a drug shortage.

In some disease settings, a new technology that is not shown to provide a direct efficacy or safety advantage over available therapy may nonetheless provide an advantage that would be of sufficient public health benefit to qualify as meeting an unmet medical need. For example, in a condition for which there are approved therapies that have a modest response rate or significant

[8] e.g. progressive disability when the available therapy has shown an effect on symptoms but has not shown an effect on progressive disability

[9] e.g. superiority of the new drug used alone or in combination with available therapy in an active- or historically-controlled trial assessing an endpoint reflecting mortality or serious morbidity

heterogeneity in response, a drug with a novel mechanism of action (but comparable safety and effectiveness) could have the potential to provide an advantage over available therapy. In such a case, the novel mechanism of action should have a well-understood relationship to the disease pathophysiology. In addition, there should be a reasonable basis for concluding that a significant number of patients may respond differently to the new drug compared to available therapy. For example, mechanistic diversity, even without a documented efficacy or safety advantage, could be advantageous in disease settings in which drugs become less effective or ineffective over time. For example, infectious disease drugs or targeted cancer therapies with novel mechanisms of action, although appearing to have comparable efficacy across the disease population, could benefit patients who no longer respond to available therapy. Accordingly, FDA intends to consider a range of potential advantages over available therapy beyond those shown in head-to- head comparisons.

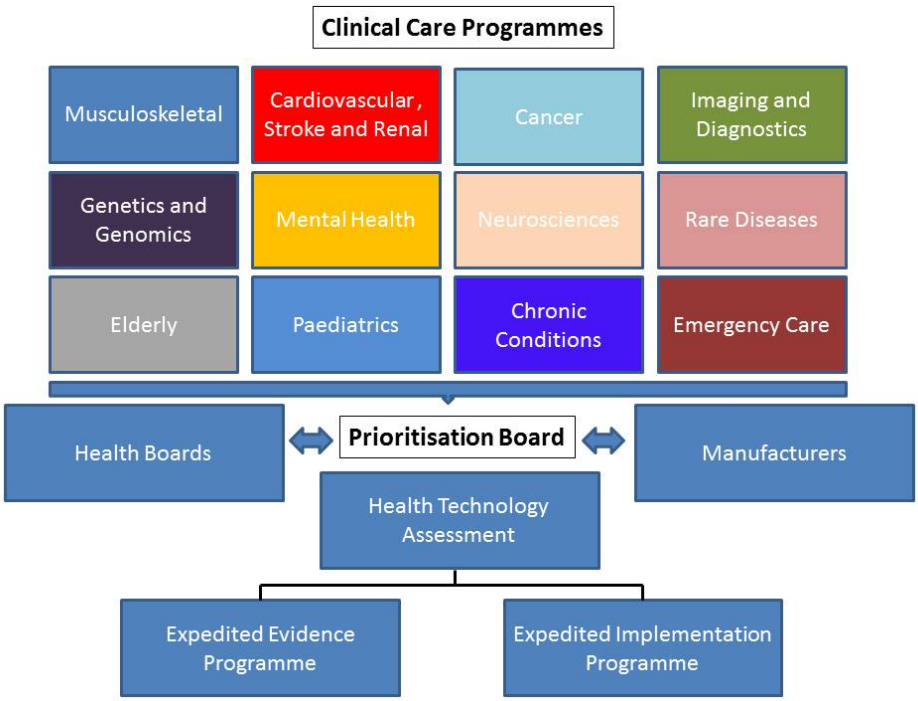
Where the Only Available Therapy Was Approved Under the Accelerated Approval Program Based on a Surrogate or Clinical Endpoint and Clinical Benefit Has Not Yet Been Verified

WHSSC recognizes, as a general matter, that it is preferable to have more than one treatment approved under the accelerated approval provisions because of the possibility that clinical benefit may not be verified in post-approval confirmatory trials. The Agency may therefore consider products as addressing unmet medical need notwithstanding the availability of therapies with accelerated approval.

VI. OVERVIEW OF THE THREE EXPEDITED EVIDENCE PROGRAMS

The table below provides an overview of the three expedited programs. Additional details on the specific programs are found in the sections that follow. **Figures 1 and 2** provide an overview of the collaboration required between stakeholders during Health Technology Assessment and provides a summary of the processes that should be overseen by an All Wales Agency including expedited evidence programmes: Fast Track, Breakthough Therapy and Priority Review and expedited implementation programmes: Pilot site Designation and Commissioning and Outcomes Framework.

Figure 1. OVERVIEW OF THE INTERACTION BETWEEN COLLABORATIVE STAKEHOLDERS



*Clinical care programmes are multi-disciplinary groups comprised of clinicians, patients and healthcare managers from specialised and non-specialised services backgrounds

Figure 2. OVERVIEW OF THE AGENCY FOR HEALTH TECHNOLOGY ASSESMENT AND EXPEDITED EVIDENCE AND IMPLEMENTATION PROGRAMMES

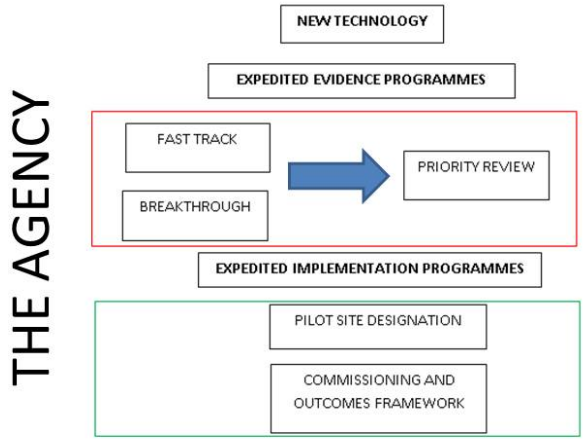


Table 1. Overview of Fast Track, Breakthough Therapy and Priority Review Programmes

	Fast Track	**Breakthrough Therapy**	**Priority Review**
Nature of program	Designation	Designation	Designation

Qualifying criteria	A new technology that is intended to treat a serious condition **AND** nonclinical or clinical data demonstrate the potential to address unmet medical need **OR** A new technology that has been designated as a qualified infectious disease product	A new technology that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	An application (original or efficacy supplement) for a drug that treats a serious condition **AND** if approved, would provide a significant improvement in safety or effectiveness **OR** Any supplement that proposes a labeling change pursuant to a report on a pediatric study **OR** An application for a drug that has been designated as a qualified infectious disease product **OR** Any application or supplement for a drug submitted with a priority review voucher
When to submit	With IND or after Ideally, no later than the pre-BLA or pre-NDA meeting	With IND or after Ideally, no later than the end-of-Phase 2 meeting	With original BLA, NDA, or efficacy supplement
Timelines for response	Within 60 calendar days of receipt of request	Within 60 calendar days of receipt of request	Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement

Features	Actions to expedite development and review Rolling review	All fast track designation features Intensive guidance on efficient drug development during IND, beginning as early as Phase 1 Organizational commitment involving senior managers	Shorter clock for review of marketing application (6 months compared to the 10-month standard review)
Additional considerations	Designation may be withdrawn if it no longer meets fast track qualifying criteria	Designation may be withdrawn if it no longer meets breakthrough therapy qualifying criteria	Designation will be assigned at the time of original BLA, NDA or efficacy supplem

VII. FAST TRACK DESIGNATION

The Agency provides for the designation of a drug as a fast track product "if it is intended, whether alone or in combination with one or more other technologies, for the treatment of a *serious or life-threatening disease or condition*, and it *demonstrates the potential to address unmet medical needs* for such a disease or condition." This section describes the qualifying criteria (italicized terms) and the features (e.g., benefits) of fast track designation. Appendix 1 describes the fast track designation process.

A. Qualifying Criteria for Fast Track Designation

1. Serious Condition
See Section III.A.

2. Demonstrating the Potential to Address Unmet Medical Need

The type of information needed to demonstrate the potential of a drug to address an unmet medical need will depend on the stage of drug development in which fast track designation is requested. Early in development, evidence of activity in a nonclinical model, a mechanistic rationale, or pharmacologic data could be used to demonstrate such potential. Later in development, available clinical data should demonstrate the potential to address an unmet medical need. See Section III.C.

B. Features of Fast Track Designation

1. Actions to Expedite Development and Review

There are opportunities for frequent interactions with the review team for a fast track product. These include -sponsor meetings, including pre-IND, end of Phase 1, and end of Phase 2 meetings to discuss study design, extent of safety data required to support approval, dose-response concerns, use of biomarkers, and other meetings as appropriate (i.e., to discuss accelerated approval, the structure and content of an NDA, and other critical issues).

In addition, such a product could be eligible for priority review if supported by clinical data at the time of BLA, NDA, or efficacy supplement submission.

2. Submission of Portions of an Application (Rolling Review)

If The Agency determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the Agency shall evaluate for filing, and may consider reviewing portions of a marketing application before the sponsor submits the complete application.

VIII. BREAKTHROUGH THERAPY DESIGNATION

This paper suggests a provision for designation of a new technology as a breakthrough therapy "if the new technology is intended, alone or in combination with 1 or more other technologies, to treat a *serious or life-threatening disease or condition* and *preliminary clinical evidence* indicates that the new technology may demonstrate substantial improvement over *existing therapies* on 1 or more *clinically significant endpoints*, such as substantial treatment effects observed early in clinical development." This section describes the qualifying criteria (italicized terms) and the features (e.g., benefits) of breakthrough therapy designation. Appendix 1 describes the breakthrough therapy designation process.

A. Qualifying Criteria for Breakthrough Therapy Designation

1. Serious Condition: See Section III.A. 274

2. Existing (or Available) Therapies: See Section III.B. 278

3. Preliminary Clinical Evidence

Unlike the information that could support fast track designation, which could include theoretical rationale, mechanistic rationale (based on nonclinical data), or evidence of nonclinical activity, breakthrough therapy designation requires preliminary clinical evidence of a treatment effect that would represent substantial improvement over available therapies for the treatment of a serious condition. Assessment of the treatment effect for the purposes of breakthrough therapy designation will be based on preliminary clinical

evidence, which could include early clinical evidence of both clinical benefit and an effect on a mechanistic biomarker (generally derived from Phase 1 and 2 trials). Nonclinical information could support the clinical evidence of drug activity. In all cases, preliminary clinical evidence demonstrating that the drug may represent a substantial improvement over available therapy should involve a sufficient number of patients to be considered credible. However, WHSSC recognizes that the data cannot be expected to be definitive at the time of designation.

Ideally, preliminary clinical evidence would be derived from a study that compares the investigational intervention to an available therapy (or placebo, if there is no available therapy) in clinical testing and shows superiority, or from a study that compares the new treatment plus SOC to the SOC alone. The Agency should have the remit to encourage sponsors to obtain some preliminary comparative data of this kind early in development. Other types of clinical data that could also be persuasive include studies comparing the new treatment with historical experience (generally, The Agency established should expect such data would be persuasive only if there is a large difference between the new treatment and historical experience).

4. May Demonstrate Substantial Improvement on Clinically Significant Endpoint(s)

To support a breakthrough therapy designation, the preliminary clinical evidence must show that the new technology may demonstrate "substantial improvement" over available therapy on one or more "clinically significant" endpoints.

Substantial Improvement: To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy. Such improvement will be clear when there is no available therapy or when available therapy shows only a modest response and the new therapy shows an effect on an important outcome. Where there is an effective available therapy, showing substantial improvement is more challenging.

Approaches to demonstrating preliminary clinical evidence of substantial improvement include:

•Direct comparison of a new technology to available therapy (or to no treatment if none exists) showing a much greater or more important response (e.g., complete response where the control treatment results in partial response). Such a trial could be conducted in treatment naïve patients or in those whose disease failed to respond to available therapies either as a

comparison with the failed therapy (if ethically acceptable) or as a no-treatment controlled study.

•The new technology added to available therapy results in a much greater or more important response compared to available therapy in a controlled study or to a historical control. This trial also could be conducted in treatment naïve patients or in those whose disease failed to respond to available therapies.

•The new technology treats the underlying cause of the disease, in contrast to available therapies that treat only symptoms of the disease, and preliminary clinical evidence shows significant efficacy. In this case, the treatment effect is entirely new (i.e., has not been observed with available therapies). For example, a drug that targets a defective protein that is the underlying cause of a disease (whereas current therapies only treat the symptoms of the disease).

•The new drug reverses disease progression, in contrast to available therapies that only provide symptomatic improvement.

•The new drug has an important safety advantage that relates to serious adverse events compared to available therapies and has similar efficacy.

Clinically Significant Endpoint: For purposes of breakthrough therapy designation, the Agency may consider *clinically significant endpoint* generally to refer to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. It can also refer to findings that suggest an effect on IMM or serious symptoms, including:

•An effect on an established surrogate endpoint
•An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
•An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
•A significantly improved safety profile compared to available therapy (e.g., less dose- limiting toxicity for an oncology agent), with evidence of similar efficacy

In a breakthrough therapy designation request, the sponsor should provide justification for why the endpoint, biomarker, or other findings should be considered clinically significant.

B. Features of Breakthrough Therapy Designation

1. All Fast Track Designation Features

A new technology that qualifies for breakthrough therapy designation would also meet the standard for fast track designation[10]. The Agency should however also determine that it would be appropriate for the features of fast track designation to be available to a drug designated as a breakthrough therapy (see Section V.B).

2. Intensive Guidance on an Efficient Drug Development Program, Beginning as Early as Phase 1

As discussed previously, breakthrough therapy designation will usually mean that the effect of the drug will be large compared to available therapies. In such cases, the development program for the breakthrough therapy could be considerably shorter than for other drugs intended to treat the disease being studied. However, FDA notes that a compressed drug development program still must generate adequate data to demonstrate that the drug is safe and effective in order to meet the statutory standard for approval. Omitting components of the drug development program that are necessary for such a determination can significantly delay, or even preclude, implementation approval.

Sponsors can design an efficient clinical trial or trials in a number of ways. The Agency should seek to ensure that the sponsor of a product designated as a breakthrough therapy receives timely advice and interactive communications in order to help the sponsor design and conduct a development program as efficiently as possible. During these interactions, the Agency may suggest, or a sponsor can propose, alternative clinical trial designs[11]

It is anticipated that the review team and the sponsor will meet throughout drug development to address these and other important issues at different phases of development. In addition, a sponsor should be prepared for a more rapid pace for other aspects of the drug development (e.g. manufacturing (see Section IX.A), development of a necessary companion diagnostic).

3. Organizational Commitment Involving Senior Managers

[10] e.g. Section 902 of FDASIA instructs FDA to take actions appropriate to expedite the development and review of a breakthrough therapy

[11] e.g. adaptive designs, an enrichment strategy, use of historical controls) that may result in smaller trials or more efficient trials that require less time to complete. Such trial designs could also help minimize the number of patients exposed to a potentially less efficacious treatment (i.e., the control group treated with available therapy).

The Agency should intend to expedite the development and review of a breakthrough therapy by, where appropriate, intensively involving senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review. Where appropriate, the Agency should to assign a cross-disciplinary project lead for the review team to facilitate an efficient review of the development program. The cross-disciplinary project lead will serve as a scientific liaison between the members of the review team (e.g., clinical; pharmacology-toxicology; chemistry, manufacturing, and controls (CMC); compliance; biostatistics) for coordinated internal interactions and coordinated communications with the sponsor through the review division's Regulatory Health Project Manager (see **Figure 1** for clinical programmes).

If a sponsor has not requested breakthrough therapy designation, the Agency may suggest that the sponsor consider submitting a request if: (1) after reviewing submitted data and information (including preliminary clinical evidence), the Agency thinks the drug development program may meet the criteria for breakthrough therapy designation and (2) the remaining drug development program can benefit from the designation.

IX. PRIORITY REVIEW DESIGNATION

An application for a new technology will receive priority review designation if it is for a drug that treats a *serious condition* and, if approved, would *provide a significant improvement in safety effectiveness*. In addition, there are specific statutory provisions that provide for priority review for various types of applications, described in Section IV. A priority designation is intended to direct overall attention and resources to the evaluation of such applications. This section describes the qualifying criteria (italicized terms) and the features (e.g., benefits) of priority review designation. Appendix 1 describes the priority review designation process.

A. Qualifying Criteria for Priority Review Designation

1. Serious Condition: See Section III.A.

2. Demonstrating the Potential To Be a Significant Improvement in Safety or Effectiveness

On a case-by-case basis, The Agency would determine whether the proposed new technology would be a *significant improvement* in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. Significant improvement may be illustrated by the following examples:

•Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition;
•Elimination or substantial reduction of a treatment-limiting drug reaction;

•Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes;
•Evidence of safety and effectiveness in a new subpopulation

Although such evidence can come from clinical trials comparing a marketed product with the investigational technology, a priority review designation can be based on other scientifically valid information. Generally, if there is an available therapy (see Section III.B), sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority related to either safety or effectiveness. Alternatively, sponsors could show the ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy. Although such showings would usually be based on randomized trials, other types of controls could also be persuasive, for example, historical controls.

B. Features of Priority Review Designation

A priority review designation means the Agencies' goal is to take action on the implementation application within 6 months (compared to 10 months under standard review).

X. GENERAL CONSIDERATIONS

Communication with the Agency is a critical aspect of expedited programs. The Agency should strive to provide a timely response to a sponsor's inquiry regarding an expedited development program. It is equally critical that the sponsor respond promptly to the Agencies inquiries. This applies to formal meetings and related inquiries, written correspondence, and other interactions. In addition to the many types of formal meetings[33] and correspondence the Agency offers to sponsors, additional considerations for sponsors of expedited programs are highlighted in this section.

A. Manufacturing and Product Quality Considerations

The sponsor of a product that receives an expedited drug development designation will probably need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program. The sponsor's product quality team and clinical programme teams should initiate early communication with the Agency to ensure that the manufacturing development programs and timing of submissions meet the Agency's expectations for licensure or marketing approval.

When sponsors receive an expedited drug development designation, they should be prepared to propose a commercial manufacturing program that will ensure availability of quality product at the time of approval. The proposal should consider estimated market demand and the commercial

manufacturing development plan, especially with regard to manufacturing facilities, lifecycle process validation (including scale-up and comparability), methods validation, stability studies, and potency studies if applicable. The proposal should also include a timeline for development of the manufacturing capabilities with goals aligned with the clinical development program. The applicant should ensure that the manufacturing process is sufficiently developed in order to support the clinical programme team section. After the initial discussion following designation, frequent communication during development will generally facilitate meeting manufacturing development and product quality goals.

The sponsors of such products should allow for an earlier submission of the clinical programme team section (including product quality information) for timely review, and, critically, for inspection planning. Coordination with the sponsor and contract manufacturers may be necessary to ensure facilities (e.g., the manufacturing process and equipment) are ready for inspection (e.g., during review of the clinical section of the application). A comprehensive meeting with the Agencies product quality review and evaluation offices in advance of submission may facilitate quality assessment of products designated for expedited programs.

B. Non-clinical Considerations

To ensure timely submission and review of nonclinical data, sponsors should initiate early communication with The Agency for their non-clinical study programs. Considerations, such as study protocol modifications, sequence and scheduling of studies, and the need for specific studies (e.g., long-term side effects / toxicity), may be important in the context of expedited new technologies development. The Agency will provide guidance to sponsors on the development of appropriate and timely non-clinical data needed to support an application for marketing approval or licensure.

C. Clinical Inspection Considerations

Sponsors should anticipate the Agency's need to inspect clinical trials, including, if applicable, the analytical component of bioavailability or bioequivalence studies. Inspections should be scheduled early in the application review process so inspection results are available to inform the review division and to allow time for the sponsor to address significant inspection findings. To select sites for clinical inspections (SEE SECTION XI), it is important for reviewers to have timely access to adequate and accurate data in BLA, NDA, or supplement submissions. Sponsors should initiate early communication with FDA about information required for inspection planning and conduct.

XI. DESIGNATION OF PILOT SITES

What is the objective of designating pilot sites?

Implementing widespread uptake of new technologies developed via the 'Fast Track', 'Breakthough' and 'Prioritised Review' processes carries potentially significant clinical and operational risks. The nature of these programmes and the potential paucity of good quality evidence necessitates that dissementation and use of new technologies through these routes need to be controlled in a clinically well regulated manner.

Designating pilot sites within an agreed commissioning and outcomes framework (See section XII) will also mandate:

- operating a single audit program that provides confidence in program outcomes;
- to enable the appropriate regulatory oversight of medical device manufacturers' quality management systems, while minimizing regulatory and industry burdens;
- promote more efficient and flexible use of regulatory resources through work-sharing and mutual acceptance among regulators (e.g. CTE process in NHS England), while respecting the sovereignty of each authority;
- to leverage, where appropriate, existing conformity assessment structures;
- to promote, in long term, greater alignment of regulatory approaches and technical requirements globally based on international standards and best practices;
- to promote consistency, predictability and transparency of regulatory programs.

XII COMMISSIONNING AND OUTCOMES FRAMEWORK

Routine outcomes measurement is central to improving service quality - and accountability.

It ensures the person having access to new technologies and the clinicians offering it have up-to-date information on an individual's progress, which is of therapeutic value in itself. At an overview level, where individual patients are anonymised, service providers and commissioners can see a performance pattern for the service.

Outcome Measures in Perspective

Measuring health outcomes is central to assessing the quality of care. Outcomes can include a vast range of health states; mortality, physiologic measures such as blood pressure, laboratory test results such as serum cholesterol, patient-reported health states such as functional status and symptoms may all be used as outcome measures. Outcome measures in different contexts, such as quality improvement, public reporting, and incentive programs, can be controversial

because inferences from health states to quality are sometimes difficult to make. Interpretations may differ regarding the degree to which a specific health outcome is attributable to the antecedent health care received by a patient as opposed to other factors, including some unrelated to health care. For instance, determinants of outcomes after heart attack include patient age, gender, severity of coronary artery occlusion, prior heart attacks, and other complicating conditions, such as hypertension, diabetes, or obesity. In addition, a variety of health care services can be major determinants or contributors to an outcome. For heart attack outcomes, these could include services delivered by emergency medical technicians in the field, emergency room (ER) teams, inpatient and cardiac catheterization laboratory staff — including physicians, specialists, and nurses — and rehabilitation professionals. Attributing outcomes after heart attack to specific health care services or to specific providers in a context such as this proves challenging.

Using Outcome Measures

The need to account for all factors that influence a patient's health outcome can be addressed by adjusting for risk factors, using statistical adjustment, or stratification of the data. This adjustment will be based ideally on the state of the patient before the patient received a particular set of health care services. The timing of measurement of an outcome relative to the care received is important to interpreting a professional's contribution to an outcome (the "marginal health benefit" added to the outcome by this phase of care). For instance, the outcomes of hip replacement may be quite different at three months, one year, or five years after surgery. In some recent examples, failures of surgical technique or selected prostheses only became apparent ten years after surgery. Long-term outcomes remain difficult to measure due to the expense of locating patients for measurement.

Users of outcome measures may wish to consider other important technical questions. For instance, are the sample sizes adequate to allow sufficient adjustment for risk factors? Measured health outcomes after surgery are more statistically reliable for a surgeon performing hundreds of procedures than for a surgeon performing fewer than ten. Surgeons who perform few procedures are typically excluded from comparisons because of small sample sizes, even though users have an interest in comparing the performance of low-volume surgeons with that of other surgeons.

Outcomes measures can be very useful in quality improvement programs, by pointing out the areas in which intervention could improve care. For instance, poor stroke outcomes could result from patients' delays in recognizing symptoms, delays in emergency transport, or delays in patient assessment and treatment on arrival at the hospital. Improvement efforts can then target the areas where improvement might yield the best results. For instance, patient-originated delays might be addressed with community-based education, whereas delays attributable to emergency services could be addressed with education of technicians and/or re-organization of emergency services.

In the face of technical difficulties and the cost of collecting health outcomes data from patients directly, many "outcome measures" actually use processes of

care or use of services as "proxies" for patient's health states. For example, hospital readmission rate is sometimes referred to as an outcome measure; the underlying theory is that readmission reflects a change in health state. In reality, readmissions can occur for many reasons other than the health state of the patient. A high readmission rate may indicate that the patient's health has deteriorated, or it could indicate another issue, such as a lack of caregivers in the home or a mis-judgment about the discharge destination at the time of discharge. A high rate of readmissions could reflect poor care during the first admission, or superior care leading to rescue and a sicker population on average at discharge. Such measures may be considered "proxies for health outcome."

A clinical sponsor group (i.e. specialist interested in the new technology and potential designate pilot sites) should be responsible for agreeing with The Agency the prospective clinical outcome measures that will be recorded.

Summary

Overall, users may prefer to use outcome measures in accountability programs only if they include relatively large numbers of patients, an entity such as an accountable care organisation that can take responsibility for coordinating services, and adequate data for risk adjustment. In quality improvement programs where outcomes can be used to guide investigation and changes to the delivery process, their use is probably less controversial.

Questions to Consider When Selecting a Measure of Outcome

1. Are the outcome measures to be used for quality improvement or accountability or both criteria?
2. At what point in an episode of care is the outcome measured?
3. What other organizational and non-health care factors may influence the relationship between process of care and the outcome?
4. Can one clearly define the organisations, professionals, and staff who influence the observed outcome?

XII CONCLUSIONS

The principles, key concepts, processes and methods outlined in this paper are very different from those currently in place in NHS Wales. They reflect key components of several international institutions such as the US, Canada, New Zealand and Australia as well as the experience of several European jurisdictions.

The paper does reflect a strong collaborative approach involving a much wider range of stakeholders in the identification, prioritisation, rapid assessment, and implementation of new technologies which are considered to bring about significant improvements in the management of patients in NHS Wales.

These changes, if they are considered as having merit, cannot be achieved by merely expanding existing organisations (such as AWMSG) as they reflect a very different approach than the processes currently established in NHS Wales and England. In the opinion of the authors of this document, this will have to be

established through and collaborative and agreed strategic mandate at Ministerial level.