Get Real

Real-Life Data in Drug Development

GetReal - Project No. 115546

WP1: Deliverable D1.5: Early use of pragmatic designs in medicine development

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1. Executive Summary

This document reviews the use of pragmatic clinical trials (PCTs) conducted prior to marketing authorisation as sources of data on relative effectiveness that can be used in regulatory health authority and/or reimbursement decision-making. The effectiveness challenges for chronic obstructive pulmonary disease (COPD) therapies and the Salford Lung Study are presented as an example in this regard. This material was used to inform discussions in a GetReal workshop held on 9 September 2015. Whilst COPD therapies and the Salford Lung Study provided specific background to facilitate discussions around early PCTs, the discussion points are applicable to the use of PCTs more widely.

This document provides, a background on COPD is provided including disease epidemiology and burden as well as the current treatment options available in Europe. Since the case study focussed on effectiveness issues in COPD, the results of an extensive review of publically available regulatory and HTA documents is also included. Lastly, a brief overview of PCTs and the role of Real World Data in drug development is provided which specifically focusses on the Salford Lung Study and the Parallel Scientific Advice offered by NICE and the MHRA for this study.

2. Pragmatic clinical trials and the Salford Lung Study

2.1. GetReal Project and Work Package 1 (WP1) case studies

The overall aim of the GetReal programme is to show how robust new methods of real-world evidence (RWE) collection and synthesis could be used earlier in medicines development to support the healthcare decision making process. This depends on a shared understanding of relative effectiveness (RE), the best evidence for assessing RE, and how RWE can be incorporated into the evidence generation process before market authorisation. The overall vision of GetReal is for healthcare decision makers to have more relevant evidence to assess the added value (in particular the relative efficacy/effectiveness) of new medicines, and pharmaceutical R&D to have better insight into which studies to include in RWE generation plans that are scientifically robust and more likely to meet the needs of healthcare decision makers.

GetReal Glossary:

Real-world data (RWD): *an umbrella term for data regarding the effects of health interventions (e.g. benefit, risk, resource use, etc) that are not collected in the context of conventional randomised controlled trials. Instead, RWD is collected both prospectively and retrospectively from observations of routine clinical practice. RWD can be obtained from many sources including patient registries, electronic medical records, and observational studies.*

Real-world evidence (RWE): *the evidence derived from the analysis and/or synthesis of real-world data (RWD).*

For more information on RWD please refer to section 5.

The aim of GetReal Work Package 1 (WP1) is to develop a common understanding amongst healthcare decision makers and pharmaceutical R&D of the acceptability and usefulness of innovative development programmes which use real-world data to estimate the effectiveness of new medicines. The use of such data is likely to be most valuable where it is anticipated that relative effectiveness estimates based on conventional (randomised controlled trial-centred) approaches may be challenged by regulators or reimbursement bodies.

The centrepiece of GetReal WP1 is a series of disease area case studies, consisting of one or two workshops in which:

- 'Effectiveness challenges' experienced by previous medicines seeking authorisation and reimbursement are identified and understood
- Potential uses of RWE to address such challenges are considered
- Illustrative examples, analyses or simulations are described or undertaken to demonstrate these particular uses of RWE

- The value and acceptability of these analyses is assessed by different stakeholders: pharma R&D, regulators, reimbursement/HTA bodies, including the perspectives of patients and clinicians

Learnings from each case study are reported separately; they are also used to inform guidance on the use of RWE in medicine development and approval, to be organised within a decision framework being developed by GetReal WP1.

2.2. Chronic Obstructive Pulmonary Disease (COPD)

In the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, COPD is defined as a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases (GOLD 2015). The main symptoms include dyspnoea, cough and sputum production. Exacerbations often occur, where there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations (NICE 2010).

2.2.1. Epidemiology and burden:

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing (GOLD 2015).

In 2008, global COPD prevalence was estimated at 210 million with an annual mortality of 3 million, affecting both developed and developing countries (WHO 2008). There is a high risk of under diagnosis in COPD, 60-80% of patients, mainly with mild to moderate disease, are thought to remain undiagnosed (Decramer 2012).

Besides the substantial humanistic burden, the economic burden to healthcare providers and society as a whole is substantial with direct costs estimated at €38.6 billion in the EU and $29.5 billion in the US (GOLD 2010). In the EU, this translates to a 6% share of the total healthcare budget and 56% of the total costs of respiratory disease (GOLD 2015).

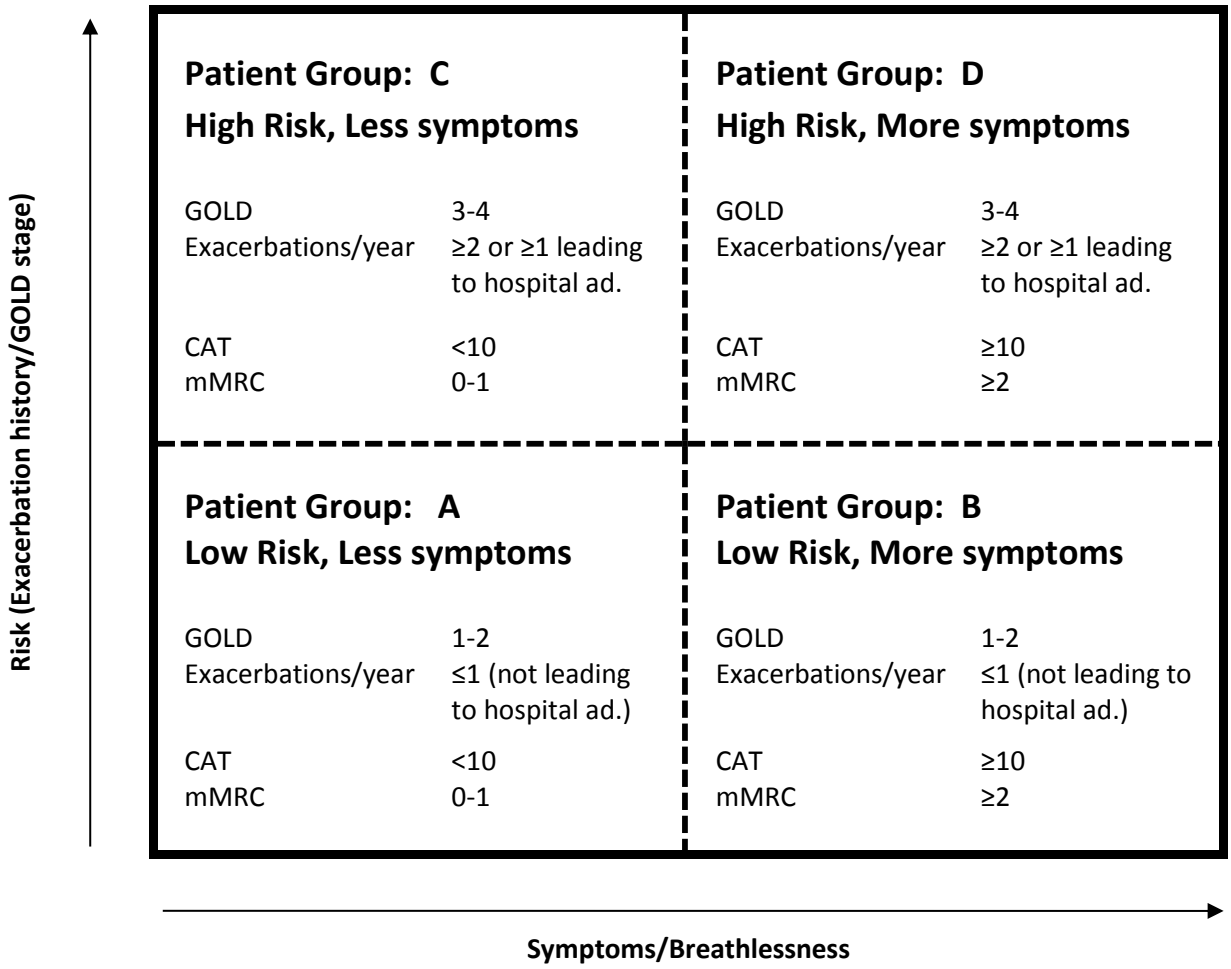
2.2.2. Clinical management & Treatment:

The goal of treatment in stable COPD is to reduce the symptoms and risks of the disease, to improve health status and exercise tolerance, reduce the frequency and severity of exacerbations, prevent disease progression and reduce patient mortality (GOLD 2015).

The GOLD combined symptom/risk assessment is commonly referred to in the management of COPD (Figure 1). This approach groups patients based on an assessment of symptoms and exacerbation risk. The 4 groups identified support the pharmacologic management of COPD (Figure 2) which is predominantly based around short and long acting bronchodilators and inhaled steroids.

Figures 1 & 2 Adapted from: Global Initiative for Chronic Obstructive Lung Disease. GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (updated 2015) for the use of the IMI-GetReal WP1 COPD Workshop alone. Accessible at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf

Figure 1. Model of Symptom/Risk Evaluation of COPD



GOLD stage: Classification of airflow limitation based on post-bronchodilator FEV1; Exacerbation: An acute event characterized by a worsening of the patients respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication; CAT: COPD Assessment Test; mMRC: modified British Medical Research Council Questionnaire;

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106 Figure 2. Pharmacologic Management of COPD

Patient Group	Recommended First Choice	Second Choice	Other possible treatments
A	SABA prn *or* SAMA prn	LABA *or* LAMA *or* SABA + SAMA	Theophylline
B	LABA *or* LAMA	LAMA + LABA	SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA + LABA *or* LAMA +PDE-4 inhibitor *or* LABA + PDE-4 inhibitor	SABA *and/or* SAMA Theophylline
D	ICS + LABA *and/or* LAMA	ICS + LABA + LAMA *or* ICS + LABA + PDE-4-inhibitor *or* LAMA + LABA *or* LAMA + PDE-4-inhibitor	Carbocysteine N-acetylcysteine SABA *and/or* SAMA Theophylline

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108 SABA: Short acting beta-agonist (e.g. salbutamol); LABA: Long-acting beta agonist (e.g. salmeterol); SAMA:
109 Short-acting muscarinic antagonist (anticholinergics) (e.g. ipratropium); LAMA: Long-acting muscarinic
110 antagonist (e.g. tiotropium); ICS: Inhaled corticosteroids (e.g. budesonide); PDE-4: Phosphodiesterase-4

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2.3. COPD Therapies

Table 1 presents a summary of COPD Therapies assessed in the last 5 years together with the Regulatory and HTA milestones. These medicines formed the basis for the review of efficacy and effectiveness challenges presented in Section 4 of this report.

Table 1: Summary of Therapies reviewed and Regulatory and HTA milestones

PRODUCT NAME	INN (Class)	MAH	Regulatory Body / MA date	ZIN	HAS	IQWiG	SMC*	CADTH
Onbrez / Oslif / Hirobriz	INDA (LABA)	Novartis	EMA: NOV-2009	STA – MAY 2010	STA – DEC 2010	N/A	STA – AUG 2010	CDR – AUG 2012
Bretaris / Eklira	ACLID (LAMA)	AZ	EMA: JUL-2012	N/A	STA– APR 2013	STA – DEC 2012	STA – NOV 2012	N/A
Seebri / Tovanor / Enurev	GLYP (LAMA)	Novartis	EMA: SEP-2012	STA – DEC 2012	N/A	N/A	STA – JAN 2013	CDR – MAY 2013
Ultibro / Ulunar / Xoterna	GLYP/IND (LAMA+LABA)	Novartis	EMA: SEP-2013	N/A	STA – MAY 2014	STA – FEB 2014	STA – DEC 2014	CDR – DEC 2014
Relvar	FF/VI (ICS+LABA)	GSK	EMA: NOV-2013	STA – MAR 2014	N/A	N/A	STA – APR / JUN 2014	N/A
Striverdi	OLOD (LABA)	B-I	NA: FEB-2014	STA – FEB 2014	N/A	N/A	STA – AUG 2014 / JAN 2015	N/A
Incruse	UMEC (LAMA)	GSK	EMA: APR-2014	STA – MAR 2015	N/A	N/A	STA – DEC 2014	CDR – MAR 2015
Anoro / Laventair	UMEC/VI (LAMA+LABA)	GSK	EMA: MAY-2014	STA – SEP 2014	N/A	STA – OCT 2014	STA – FEB 2015 (resub.)	CDR – JAN 2015
Brimica / Duaklir	ACLID/FOR (LAMA+LABA)	AZ	EMA: NOV-2014	ESNM57 – APR 2015	N/A	N/A	STA – APR 2015	STA – APR 2015

N/A = not available; STA = Single Technology Appraisal; CDR: Common Drug Review; MA = marketing authorisation; EMA = European Medicines Agency; NA = National Authorities (via the decentralise procedure); NICE = National Institute for Health and Care Excellence (England & Wales); SMC = Scottish Medicines Consortium (Scotland); HAS = Haute Autorité de Santé (France); ZIN = Zorginstituut Nederland (Netherlands);

* In the UK, NICE did not perform technology appraisals for the listed medicines. A series of Evidence summaries for New Medicines (ESNM) have been published but these (describe in one sentence).

2.3.1. Efficacy and effectiveness data

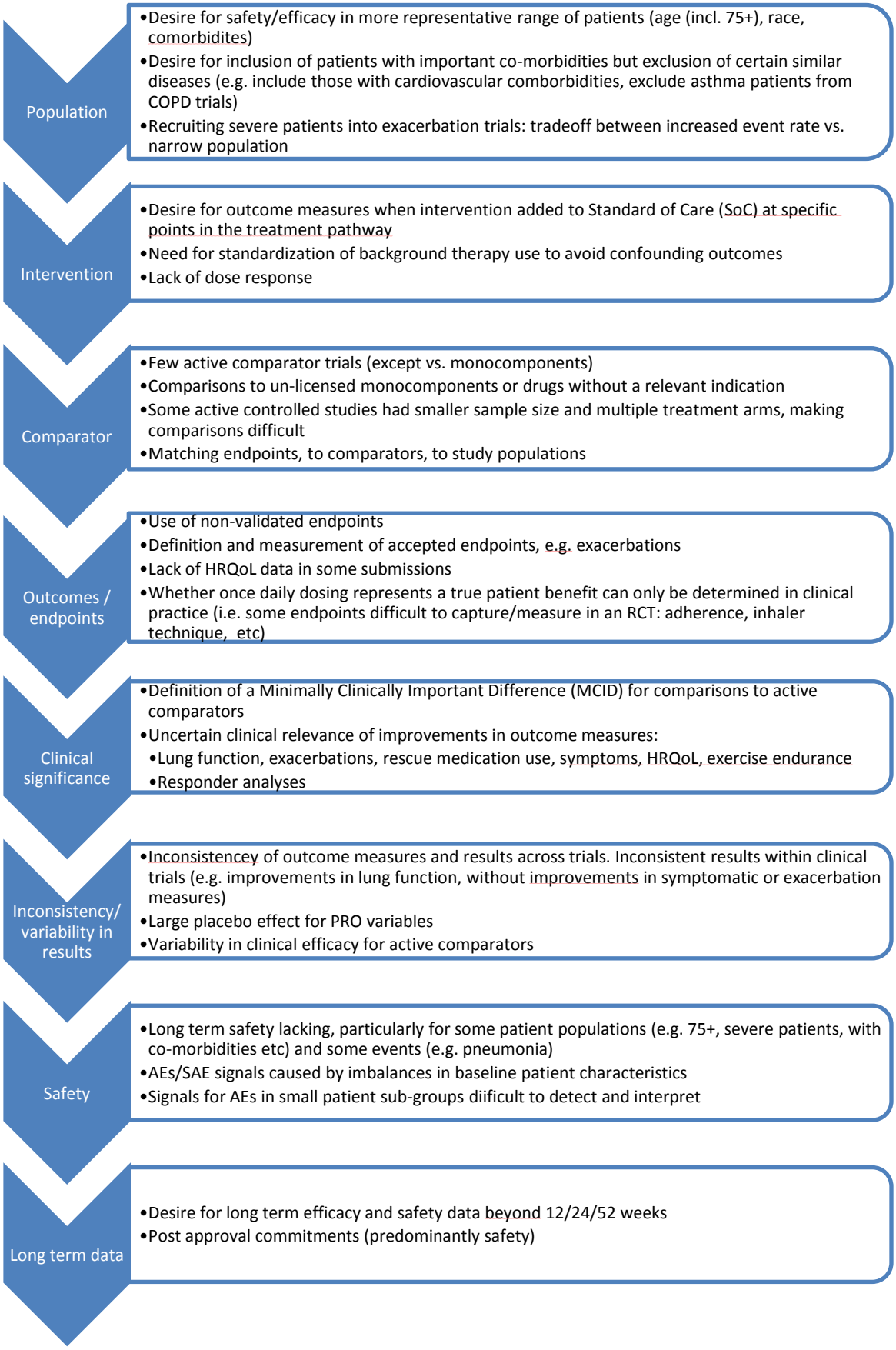
A review of European Regulatory and HTA decisions for the COPD therapies identified in Table 1 was carried out by Context Matters to identify key issues/uncertainties encountered during the assessments of these medicines. Further details of the outputs of these reviews can be found in Appendix A.

The review sought to identify any efficacy/effectiveness challenges reported in the publically available material and so is not considered a comprehensive list. Furthermore, the findings may not all be those which can be addressed by early PCTs but are included to enable discussions on this subject.

2.3.2. EPAR review

The following section provides a summary of the findings identified from European Public Assessment Reports (EPARs).

138 ***EPAR Review - Summary of EMA Challenges for 10 recent drug approvals in COPD***



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2.3.3. HTA review

A report prepared by Context Matters (Appendix A) summarises uncertainties in the clinical evidence raised during regulatory and reimbursement assessments for COPD drugs approved by the EMA, Health Canada (HC), and/or the Therapeutic Goods Administration (TGA) between 2010 and 2015.

Public assessments from NICE, SMC, HAS, G-BA/IQWiG, CADTH, and PBAC were analysed and the following key themes of clinical uncertainty were identified:

Lack of appropriate end points

This includes the omission of such required end points as morbidity and mortality, but in many cases, the agency was interested in patient-centred outcomes such as activities of daily living (ADLs), health-related quality of life (HRQoL), exacerbations, and symptoms, which were not the main focus in the clinical trials.

Clinically significant vs. statistically significant results

Agencies discussed clinically significant results in end points such as forced expiratory volume in one second (FEV1) and HRQoL, noting that their statistical significance did not translate into clinically meaningful results for the patients in the studies.

Study population issues

Study populations often excluded certain groups (e.g., excluded patients with certain comorbidities or severity of disease), or were not comparable to the patient population in clinical practice. The non-generalisability problem appeared in several HTAs, and called into question the applicability of the outcomes to "real-life" in those countries.

Short-term efficacy data

Several agencies expressed concern about the relatively short length of the studies submitted, and their inability to accurately capture important facets of a chronic condition such as COPD.

Inappropriate comparators

The majority of clinical trials used placebo as the comparator, and many HTA agencies were concerned with the lack of an active comparator.

Lack of efficacy evidence in treatment pathway or with combination therapies

The drugs assessed were approved for a specific line of therapy or to be taken in combination with other therapies, but the clinical data often did not include efficacy evidence in the country's specific treatment pathway or in combination with the other therapies.

Weight of clinical uncertainty on the final outcome of the HTA

While there are significant similarities among the HTA agencies in what they note as clinical uncertainties, it is important to note that HTA agencies have different remits, review processes, and values. These differences can lead to certain areas of clinical uncertainty having more weight than others. For example, part of G-BA's assessment process is to determine the "appropriate comparator therapy" and this comparator must be used in the HTA evaluation. If the manufacturer submits the clinical evidence with a different comparator than the G-BA determined "appropriate comparator", G-BA is likely to conclude that there was no evaluable evidence and the drug will likely be given a "no additional benefit" score. Similarly, head-to-head active comparator trials are preferred by all the HTA agencies assessed, but some agencies are more willing to accept indirect comparison evidence (e.g., SMC) than others (e.g., HAS).

Based on the analysis, the clinical uncertainties that were key drivers of a decision for Germany were "inappropriate comparators", "lack of appropriate end points" and "study population issues" (as measured by 'additional benefit score'). For HAS, the key area of clinical uncertainty was "inappropriate comparators," as measured by ASMR score. For the other HTA agencies (especially those that evaluate cost-effectiveness) it was not necessarily clear how the clinical uncertainties drove the decision to recommend the drug or not. Further research is needed on the key clinical drivers of the reimbursement decision for SMC, NICE, PBAC and CADTH.

2.3.4. Use of Pragmatic Clinical Trials in HTAs

To determine how often, and in what manner, pragmatic clinical trials are used in HTAs, Context Matters searched across their data model, which contains 3,590 HTAs from nine HTA agencies (CADTH (Canada), G-BA/IQWiG (Germany), HAS (France), HIS (Scotland), NICE (United Kingdom), PBAC (Australia), pCODR (Canada), SMC (Scotland)), to determine how many used pragmatic clinical trials.

It was found that HTA bodies do not often assess pragmatic clinical trials. Only ten of the 3,590 assessments evaluated a pragmatic clinical trial (all post-marketing studies).

- PBAC reviewed 3 submissions that presented a PCT for Attention Deficit Hyperactivity Disorder. The results were in contention with the RCTs that were also evaluated. This is likely to be an issue when relative adherence to treatment arms differs in the pragmatic clinical trial compared to the RCT. PBAC did not accept the extent of the benefit based on the results of the open label pragmatic trial.
- HAS's review of seven submissions for Schizophrenia included three pragmatic clinical trials. HAS seemed to accept the evidence base (which also included RCTs, pharmacovigilance, and meta-analysis data), but it is unknown how much influence the pragmatic trials had on the overall conclusion.

Three additional HAS assessments called for a pragmatic clinical trial to demonstrate the drugs' efficacy in the real world. These three trials were to be post-marketing trials.

2.4. The role of Real World Data in Drug Development

Real World Data (RWD) is defined in the GetReal glossary as: *an umbrella term for data regarding the effects of health interventions (e.g. benefit, risk, resource use, etc.) that are not collected in the context of conventional randomised controlled trials. Instead, RWD is collected both prospectively and retrospectively from observations of routine clinical practice. RWD can be obtained from many sources including patient registries, electronic medical records and observational studies. [Adapted from Garrison, 2007]*

Real World Evidence (RWE) is defined as: *the evidence derived from the analysis and/or synthesis of real-world data.*

RWD covers a very wide range of categories of data and potential sources (see Table 2).

Table 2. Sources and Uses of Real World Data for Effectiveness

	Pre launch	**Post launch**
Randomised/ Interventional	***New Medicine & Usual Care:***	***New Medicine & Usual Care:***
Pragmatic Clinical Trial *(see section 6)*	Clinical Effectiveness Outcomes Health-related Quality of Life Patient Behaviour Resource use	Clinical Effectiveness Outcomes Health-related Quality of Life Patient Behaviour Resource use
Non-interventional	***Usual Care Only:***	***New Medicine & Usual Care:***
Prospective Observational Study	Treatment patterns, care pathways, sequences (patient profiles) Effectiveness Outcomes Health-related Quality of Life Patient Behaviour Resource use	Treatment patterns, care pathways, sequences (patient profiles) Effectiveness Outcomes Safety Outcomes Health-related Quality of Life Patient Behaviour Resource use
Retrospective Electronic Health Records (EHR) & Disease Registries	Treatment patterns, care pathways, sequences (patient profiles) Effectiveness Outcomes Natural History of Disease	Treatment patterns, care pathways, sequences (patient profiles) Effectiveness Outcomes Safety Outcomes Natural History of Disease
Retrospective Claims databases	Treatment patterns Resource use and costs	Treatment patterns Resource use and costs
"Patient Powered" Research Registries	Patient reported Symptoms Health-related Quality of Life Patient Preferences	Patient reported Symptoms Health-related Quality of Life Patient Preferences

The traditional focus for the application of RWE in medicines development has been at three key stages.

1. to understand the natural history of disease, treatment patterns, and the resource use and cost associated with usual care: to guide the appropriate population and comparators for drug development decisions

2. to describe in more detail the treatment patterns, effectiveness outcomes, resource use and cost associated with usual care in specific populations and geographical areas: to inform effectiveness models and provide context for health technology assessments.

3. to answer post-launch questions related to drug utilisation, real world practice patterns and real world safety and comparative effectiveness. There is also increasing focus on using post launch RWE to guide optimisation of the use of medicines, through real-time monitoring of patients' treatment, health status, and care pathway.

In order to predict Relative Effectiveness at the time of initial market authorisation, from the RCT and RWE data that is available at that time, a variety of analytical techniques are used e.g.: network meta analysis, effectiveness models, predictive analytics.

GetReal is exploring how RWE can be used to better inform the understanding of Relative Effectiveness at the time of initial market authorisation by new approaches to e.g. the use of PCTs, and novel analytical techniques to more powerfully integrate RCT, PCT and Observational data.

Examples of other uses of RWD in medicine development that are not under explicit review by GetReal are the use of genomic databases to identify targets for new medicines, studies for the validation of (new) Patient Reported Outcomes, estimation of patient management costs and valuations of health outcomes, and evaluation of service delivery (optimising care pathways).

2.4.1. Pragmatic clinical trials (PCTs)

What are PCTs?

The term PCT may refer to pragmatic clinical trials or pragmatic controlled trials.

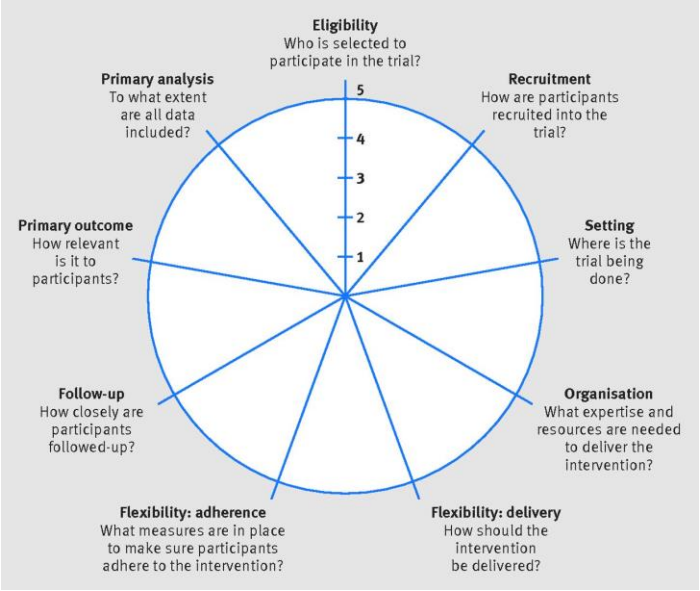
The GetReal Glossary defines a PCT as *'a study comparing several health interventions among a randomised, diverse population representing clinical practice, and measuring a broad range of health outcomes. To ensure generalizability, pragmatic trials should represent the patients to whom the treatment will be applied as best possible. For instance, inclusion criteria would be broad (e.g. allowing co-morbidity, co-medication, wider age range, etc.), the follow-up would not be (or not much) interventional and allowing for treatment switching etc. Pragmatic clinical trials are a sub-category of large simple trials.' (adapted from Schwartz 1967, Roland 1998, Tunis 2003)*

The underlying premise of PCTs is to maximise the external validity of trial results – ' does the intervention work under usual conditions?' the results should be directly applicable to decision making for the full range of patients who may benefit from the new therapy of interest, without unduly compromising internal validity resulting in the possibility of biased comparisons. Many elements of good conduct of clinical trials are preserved, such as protocol development and ethical approval, randomisation, data collection, blinding (of outcome assessment) and intention-to-treat analysis. However compared with conventional Phase 3a RCTs there may be broader inclusion criteria, involvement of a broader set of clinicians, no special strategies to ensure that physicians and subjects follow the study protocol, 'usual practice' as a comparator intervention, minimal extra visits for patient follow-up, and study outcomes meaningful to clinicians and decision-makers and not requiring specialist training.

Domains and levels of pragmatism

The PRECIS framework (Pragmatic-Explanatory Continuum Indicator Summary) was developed to help trial designers and reviewers assess the degree of pragmatism of a trial across ten domains (Thorpe 2009, Loudon 2013). The tool was recently updated and named PRECIS-2 (Loudon 2015). The degree of pragmatism can be visualised using a wheel with 9 spokes – one for each domain, where more pragmatism in any particular domain generates a point on the corresponding spoke further away from the hub, nearer the rim.

The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel (Loudon et al 2015):



Domain	Explanation
Eligibility	To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care? For example, score 5 for very pragmatic criteria essentially identical to those in usual care; score 1 for a very explanatory approach with lots of exclusions (e.g. those who don't comply, respond to treatment, or are not at high risk for primary outcome, are children or elderly), or uses many selection tests not used in usual care.
Recruitment	How much extra effort is made to recruit participants over and above what that would be used in the usual care setting to engage with patients? For example, score 5 for very pragmatic recruitment through usual appointments or clinic; score 1 for a very explanatory approach with targeted invitation letters, advertising in newspapers, radio plus incentives and other routes that would not be used in usual care.
Setting	How different is the setting of the trial and the usual care setting? For example, score 5 for a very pragmatic choice using identical settings to usual care; score 1, for a very explanatory approach with only a single centre, or only specialised trial or academic centres.
Organisation	How different are the resources, provider expertise and the organisation of care delivery in the intervention arm of the trial and those available in usual care? For example, score 5 for a very pragmatic choice that uses identical organisation to usual care; score 1 for a very explanatory approach if the trial increases staff levels, gives additional training, require more than usual experience or certification and increase resources.
Flexibility (delivery)	How different is the flexibility in how the intervention is delivered and the flexibility likely in usual care? For example, score 5 for a very pragmatic choice with identical flexibility to usual care; score 1 for a very explanatory approach if there is a strict protocol, monitoring and measures to improve compliance, with specific advice on allowed co-interventions and complications.
Flexibility (adherence)	How different is the flexibility in how participants must adhere to the intervention and the flexibility likely in usual care? For example, score 5 for a very pragmatic choice involving no more than usual encouragement to adhere to the intervention; score 1 for a very explanatory approach that involves exclusion based on adherence, and measures to improve adherence if found wanting. In some trials eg surgical trials where patients are being operated on or Intensive Care Unit trials where patients are being given IV drug therapy, this domain is not applicable as there is no compliance issue after consent has been given, so this score should be left blank.
Follow-up	How different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care? For example, score 5 for a very pragmatic approach with no more than usual follow up; score 1 for a very explanatory approach with more frequent, longer visits, unscheduled visits triggered by primary outcome event or intervening event, and more extensive data collection.
Primary outcome	To what extent is the trial's primary outcome relevant to participants? For example, score 5 for a very pragmatic choice where the outcome is of obvious importance to participants; score 1 for a very explanatory approach using a surrogate, physiological outcome, central adjudication or use assessment expertise that is not available in usual care, or the outcome is measured at an earlier time than in usual care.
Primary analysis	To what extent are all data included in the analysis of the primary outcome? For example, score 5 for a very pragmatic approach using intention to treat with all available data; score 1 for a very explanatory analysis that excludes ineligible post-randomisation participants, includes only completers or those following the treatment protocol

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More broadly it is important to think of the place of PCTs in the evidence generation strategies for new medicines. For example:

- What is the degree of consistency between PCT results and those of confirmatory (e.g. Phase 3a) RCTs and how can apparent inconsistencies be explained?
- Can results of PCTs be adapted to other populations (e.g. in other countries for which reimbursement is being sought) through re-analysis of trial data or modelling based on PCT results?

Setting up and running PCTs may be facilitated by making use of existing infrastructure and networks, such as practice- based research networks (with linked information systems, facilitating data capture) and patient powered research networks which may facilitate recruitment and help with optimising study design

PCTs in Respiratory Medicine

PCTs are of particular interest in chronic conditions such as asthma and COPD where patient adherence to new medicines (which may be addressed through different routes of administration, dosing schedules or devices) may be an issue. Modifying Phase 3 (explanatory) trials to enable them to pick up the potential impact on health effects through improved adherence may render them less useful for regulators seeking to understand the impact of a new medicine on safety outcomes and efficacy measures such as lung function or symptom control.

A well known example of a PCT reported by Price et al (2011) compared leukotrine-receptor antagonist (LTRA) therapy with inhaled glucocorticoid therapy (first line controller) in 306 primary care patients with asthma. Reported outcome measures (AQLQ, ACQ, PEF) showed similar efficacy between study groups over 2 months (equivalence proved) to 2 years of follow-up, with higher (non-statistically significant) adherence in the leukotrine group. Previous explanatory RCTs of patients with mild persistent asthma had reported mixed results with either similar or improved asthma control for glucocorticoid therapy. The authors urged caution in extrapolating RCT results to broad populations of patients treated with asthma in community settings.

'Early' use of PCTs

PCTs have mostly been introduced in the 'post-approval' environment in order to deliver information on safety, efficacy and especially effectiveness of new medicines to decision-makers. The main interest of GetReal is to understand where greater degrees of pragmatism may be valuable earlier in medicine development, through modification of Phase 3a trials designed primarily for regulatory approval (marketing authorisation), or introduction of PCTs at the Phase 3b stage (in addition to Phase 3a) with the intention of providing results in time for health technology assessments and reimbursement submissions. For Pharma R&D to consider investing more in this type of study it is important to understand the acceptability of more pragmatic study designs to different decision-makers, and to seek to reconcile the (diverging) needs and concerns of HTA and regulatory agencies. Work Package 3 of GetReal is focusing on the feasibility of conducting such studies, covering issues of study design, ethics and operationalisation in particular. By identifying operational challenges, analysing their impact on practical feasibility, acceptability, generalisability and bias of the PCT and offering solutions for operational challenges (where possible) they aim to help PCT designers to be aware of consequences of their choices & maximize the pragmatic nature of the study design while ensuring operational feasibility.

Guidance on pragmatic Phase 3 trials (Centre for Medical Technology Policy - CMTP 2010) has highlighted that it may neither be possible nor desirable to achieve high level of pragmatism across all PRECIS domains: three domains of particular importance to reimbursement decision making are generalisability of trial populations, the inclusion of active comparators and choice of relevant outcomes.

2.4.2. The Salford Lung Study

The Salford Lung Studies (SLS) are the world's first pre-licence pragmatic RCTs, with the goal of comparing the real-world effectiveness of a novel once-daily investigational treatment (LABA/ICS in the form of a vilanterol/fluticasone furoate Dry Powder Inhaler (DPI)) with the existing therapy for COPD and asthma. These are open-label phase III studies in which patients are randomised to either a continuation of their usual treatment or the novel DPI for 12 months. For COPD, the primary outcome is the rate of moderate and/or severe exacerbations. For asthma, the change in asthma control (Asthma Control Test) is used as primary endpoint. At the time of study initiation, efficacy and safety data were already available for more than 6400 patients from previously completed RCTs.

The influence of once-daily administration versus other treatment modalities is of particular interest as increased adherence could be related to improved outcomes, of which robust evidence would be valuable. The key objectives in designing and executing the SLS are to collect data with minimal disruption to normal clinical practice, include a large proportion of the local patient population, ensure adequate safety monitoring and meet all ethical and regulatory requirements.

After randomisation, both patient groups keep receiving care as usual by their own General Practitioner (GP), community pharmacist, practice nurses, etc, in order to allow for 'usual', real-world conditions. For example, patients on the novel DPI obtain their study drugs from their normal community pharmacy and GPs prescribe as usual. Formal study visits are only required at baseline and at the end of the study. A 'non-invasive' safety net is in place in the form of a quarterly telephone call, in case patients do not visit healthcare services.

In order to ensure the safety of the study population as well as not intervening with normal clinical practice, (near) real-time electronic data collection from all sources of care is necessary. Salford is a metropolitan borough of Greater Manchester with a relatively static population that is served by a single hospital, which has a pre-existing integrated electronic health record connecting this hospital with primary practices. The Salford Integrated Record (SIR) captures linked data in real time on all people accessing primary and secondary health services, leaving the SLS study-group to establish a link to the remaining data-gaps as for example out-of-hours services, deaths and visits to health services outside of Salford.

One of the challenges that had to be overcome regarded training healthcare workers who previously had little experience in (prelicence) clinical research. In total, more than 1000 pharmacists, GPs and nurses were extensively trained in good clinical practice, resulting in resource and timing challenges.

In April and December 2012, the first patients were enrolled into the COPD and asthma studies, respectively. Recruitment of 2800 COPD patients was completed in October 2014 with the results expected in 2016. Recruitment of asthma patients to the study is still ongoing (New JP 2014).

3. References

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Context Matters™

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Background

The three key markets of interest are:

- Europe
- Canada
- Australia

The GetReal Initiative is interested in understanding the challenges to evaluating efficacy/effectiveness data for recently approved COPD drugs. Are there issues with COPD submissions that pertain to applying efficacy data to the real-world/general population? Are there areas where Real World Evidence (RWE) in general and pragmatic clinical trials (PCT) specifically can help inform the reimbursement decision-making process?

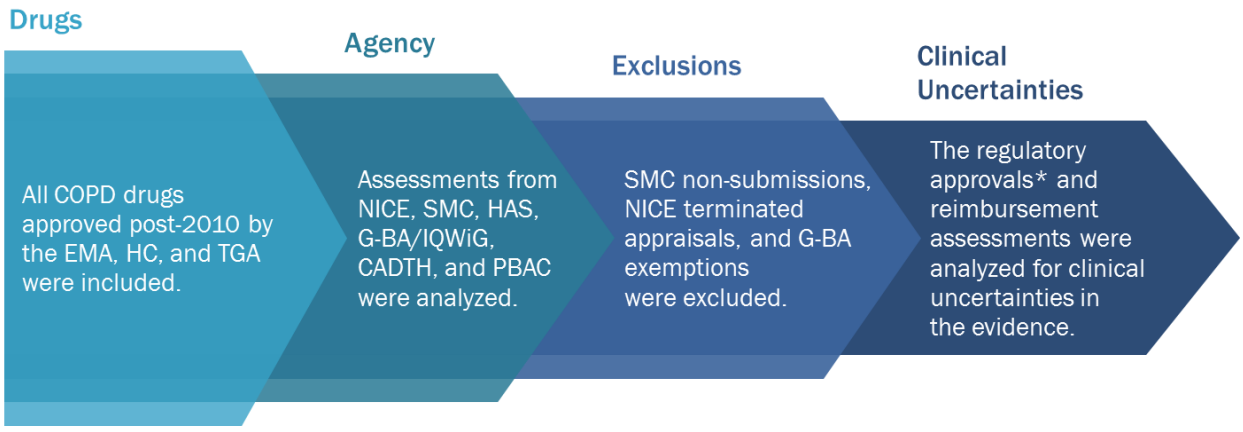
This report contains a survey of mentioned uncertainties in the clinical evidence that emerged from the regulatory and reimbursement assessments for COPD drugs approved by the EMA, Health Canada (HC), and/or the Therapeutic Goods Administration (TGA) between 2010 and 2015.

The analysis focuses on mentioned areas of clinical uncertainty and not on the methods used to mitigate this clinical uncertainty. For example, within a number of HTA evaluations, the lack of an active comparator was an area of clinical uncertainty. There were strategies employed by the manufacturer to limit the uncertainty around the comparative effectiveness (e.g., the use of indirect comparisons or network meta-analyses), but a review of the strategies employed was outside of the scope of this analysis.

It is important to note that the majority of clinical trials and assessments defined severity of COPD using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Since the GOLD criteria were not an area of clinical uncertainty mentioned within the assessments, it will not be discussed further.

Methods

55 reimbursement events and the regulatory documents for 10 COPD drugs have been included in the analysis



*The EMA and TGA Public Assessment Reports and the Health Canada Summary Basis of Decision documents were analyzed for any discussion on clinical uncertainties. These documents reflect the current uncertainties at the time of approval.

COPD Drugs

List of drugs approved 2010 - 2015 that were included in the analysis

Drug	EMA Approval	HC Approval	TGA Approval
Aclidinium bromide	2012	2013	2012
Aclidinium bromide-formoterol	2014	2015	Not approved yet
Fluticasone furoate-vilanterol	2013	2013	2014
Glycopyrronium	2012	2013	2011
Indacaterol	Approved prior to 2010	2011	2010
Indacaterol-glycopyrronium	2013	2014	2014
Olodaterol	Not approved*	2013	2014
Roflumilast	2010	2010	2011
Umeclidinium bromide	2014	2015	2015
Umeclidinium-vilanterol	2014	2013	2015

*Olodaterol has not gone through the mutual recognition procedure, thus it has not been reviewed by the EMA. Olodaterol has been approved in France and Great Britain.

COPD Clinical Uncertainty

Key Insights for Clinical Uncertainties

The regulatory agencies were concerned with uncertainty in the safety the COPD drugs assessed. Uncertainty in safety was a key theme identified in all regulatory approvals, but uncertainty in adverse events (AEs) was not discussed in the HTA assessments.

Both the regulatory and HTA agencies were concerned with the clinical significance of the results. When end points met statistical significance, the regulatory and HTA agencies often questioned if the results were clinically relevant. In addition, HTA agencies were also concerned with the effectiveness of the drug in relation to accepted clinical practice in their specific country.

- HTA agencies were concerned over the lack of direct comparators, lack of patient-relevant end points, and uncertainty of the effect of the drug within treatment pathway and within combination therapies used in clinical practice.

Both the regulatory and HTA agencies discussed how surrogate end points (e.g., FEV1) are not sufficient for COPD, so the inclusion of patient-relevant end points would be beneficial in decreasing clinical uncertainty for both regulatory and HTA agencies.

The average study duration in the clinical trials was six months to evaluate efficacy and 48 - 52 weeks to evaluate safety. The EMA and the HTA agencies noted that there was considerable uncertainty in the long-term effects for this chronic condition.

Regulatory Agencies

Clinical uncertainty discussed in the EMA, HC, and TGA scientific documents

Regulatory Key Themes of Clinical Uncertainty

The EMA and TGA often discussed uncertainties in the clinical evidence, while HC did not.

Uncertainty in adverse events (AEs).

- All regulatory agencies looked at whether AEs were known or if there was information in the data that pointed towards other unfavorable effects.

Clinically significant vs. statistically significant results.

- Drugs showing a modest, but statistically significant improvement were questioned as to whether they provided a clinically significant benefit to patients.

TGA was the only regulatory agency to question the effect of the drugs on the natural history of the disease and to explore how smoking status affected the efficacy of a drug.

The EMA was the only regulatory agency to note that the short-term efficacy data presented was an area of concern.

While only a few regulatory approvals evaluated studies that used active comparators, the regulatory agencies did not state “comparators” as an area of uncertainty. The regulatory agencies did not discuss the use of placebo-controlled trials or active comparators with slightly different indications than the drug under review as a clinical concern.

An overview of the clinical uncertainty themes by regulatory agency

	EMA	HC	TGA
Uncertainty about “unfavorable effects”/AEs	●	●	●
Clinically significant vs. statistically significant results	●	●	●
Short-term efficacy data	●		
Combination therapy drug interactions	●		
Lack of uniform significance in the clinical results		●	
Failure to investigate effect on natural history of COPD			●
Smoking Status			●

EMA

EMA Key Areas of Uncertainty

The EMA regularly includes sections around clinical uncertainty in its evaluations

Clinically significant vs. statistically significant results

The EMA often commented on drugs that presented a statistically significant improvement, but did not provide a tangible benefit to patients with COPD. For example, a few trials had FEV1 scores with improvements of less than 10%, but the EMA questioned the clinical relevance of this improvement.

Uncertainty in the knowledge about the "unfavorable effects"/adverse events (AEs)

Unfavorable effects often resulted in a restriction on the indication, but unfavorable effects with uncertain impacts often resulted in a post authorization safety study. This was seen with cardiovascular events (such as a higher incidence of atrial fibrillation/flutter), new onset first degree atrioventricular blocks, an increase of 30 - 60 millisecond in the corrected QT interval, and in infections, including pneumonia.

Short-term efficacy data

Many approvals noted that there was limited efficacy data for the long-term effects of the approved drug. Efficacy studies often stopped at six months, whereas safety studies often continued for a year. In some cases, the CHMP noted that even these longer-term safety studies did not give good information on safety beyond the length of the study.

Combination therapy drug interactions

The EMA noted a lack of studies where the combination therapy proposed was compared to the individual monotherapies to determine the incremental efficacy of the combination. In one case, the EMA proposed that the two components of the therapy could have lost some of their effects when working in combination, and that there was uncertainty in the effect of the combination therapy.

Health Canada (HC)

HC Key Areas of Uncertainty

HC rarely discusses issues of clinical uncertainty within their Summary Basis for Decision documents

Uncertainty in adverse events (AEs)

HC noted that there was uncertainty in a number of AEs within the COPD evaluations, including carcinogenic potential and unknown effects during pregnancy. Uncertainty in AEs was consistently discussed in Health Canada approvals.

Clinically significant vs. statistically significant results

HC noted in one approval that the drug showed a modest, statistically significant improvement, but it was questioned as to whether the drug provided a clinically significant benefit to patients.

Lack of uniform significance in the clinical results

In one approval, HC noted that the drug failed to show statistical significance, while other studies for the same drug showed a statistically significant impact. While this was reported in the results, HC did not often identify this as an area of clinical uncertainty.

TGA

TGA Key Areas of Uncertainty

Newer TGA evaluations have an in-depth look at the clinical evaluation

Clinically significant vs. statistically significant results

Drugs showing a modest, but statistically significant improvement were questioned as to whether they provided a clinically significant benefit to the patients.

Failure to investigate the effect on the natural history of COPD

In one drug evaluation report, TGA noted that the efficacy of inhaled glucocorticosteroids in altering the natural history of the disease has not been demonstrated. Thus, the TGA strongly questioned the use of ICS in COPD and believed that the failure to investigate the natural history of the disease was a “curious omission for developing a new drug.”

Uncertainty in AEs

TGA noted that there was uncertainty in a number of unfavorable effects within the COPD evaluations, including increased potential heart rate effects at high overdoses, other cardiovascular risks, potential growth retardation, bone mineral density deterioration, and unknown effects during pregnancy.

Smoking status

TGA noted that in one submission, smoking status was not sufficiently explored, and that tobacco exposure during the study was not monitored nor was the use of nicotine replacement therapy. They asked the sponsor for further information, and while the sponsor did not stratify the results based on smoking status, they were able to provide enough information that showed that smoking status was similar across all groups evaluated.

HTA Agencies

HTA Key Themes of Clinical Uncertainty

Lack of appropriate end points

This includes the omission of such required end points as morbidity and mortality, but in many cases, the agency was interested in patient-centered outcomes such as ADLs, HRQoL, exacerbations, and symptoms, which were not the main focus in the clinical trials.

Clinically significant vs. statistically significant results

Agencies discussed clinically significant results in end points such as forced expiratory volume in one second (FEV1) and HRQoL, noting that their statistical significance did not translate into clinically meaningful results for the patients in the studies.

Study population issues

The study populations excluded certain groups (e.g., excluded patients with certain comorbidities or severity of disease), or were not comparable to the patient population in clinical practice. The non-generalizability problem appeared in several HTAs, and called into question the applicability of the outcomes to "real-life" in those countries.

Short-term efficacy data

Several agencies expressed concern about the relatively short length of the studies submitted, and their inability to accurately capture important facets of a chronic condition such as COPD.

Inappropriate comparators

The majority of clinical trials used placebo as the comparator, and many HTA agencies were concerned with the lack of an active comparator.

Lack of efficacy evidence in treatment pathway or with combination therapies

The drugs assessed were approved for a specific line of therapy or to be taken in combination with other therapies, but the clinical data did not include efficacy evidence in the country's specific treatment pathway or in combination with the other therapies.

Weight of clinical uncertainty on the final outcome of the HTA

While there are significant similarities among the HTA agencies in what they note as clinical uncertainties, it is important to note that HTA agencies have different remits, review processes, and values. These differences can lead to certain areas of clinical uncertainty having more weight than others. For example, part of G-BA's assessment process is to determine the "appropriate comparator therapy" and this comparator must be used in the HTA evaluation. If the manufacturer submits the clinical evidence with a different comparator than the G-BA determined "appropriate comparator", G-BA is likely to conclude that there was no evaluable evidence and the drug will likely be given a "no additional benefit" score. Similarly, head-to-head active comparator trials are preferred by all the HTA agencies assessed, but some agencies are more willing to accept indirect comparison evidence (e.g., SMC) than others (e.g., HAS).

Based on the analysis, the clinical uncertainties that were key drivers of a decision or country specific scores (i.e., additional benefit score in Germany or the ASMR score in France) for Germany were "inappropriate comparators", "lack of appropriate end points" and "study population issues". For HAS, the key area of clinical uncertainty was "inappropriate comparators." For the other HTA agencies (especially those that evaluate cost-effectiveness) it was not necessarily clear how the clinical uncertainties drove the decision to recommend the drug or not. Further research is needed on the key clinical drivers of the reimbursement decision for SMC, NICE, PBAC and CADTH.

An overview of the clinical uncertainty themes by HTA agency

	SMC N=10	HAS N=6	NICE* N=1	G-BA N=8	IQWiG N=9	PBAC N=13	CADTH N=8
Inappropriate comparators	●	●	●	●	●	●	●
Short-term efficacy data	●	●		●	●	●	●
Lack of appropriate end points	●	●			●	●	●
Study population issues	●	●			●	●	●
Lack of efficacy evidence in treatment pathway or with combination therapies	●	●	●			●	●
Clinically significant vs. statistically significant results	●		●			●	●

*Note – NICE only conducted one assessment

SMC (Scotland) 

SMC reviewed 10 drugs/indications; "Recommend with restrictions" and "Recommend" were the most prevalent decisions (50% and 40%, respectively).

COPD drugs approved 2010 - 2015; agency decision and areas of clinical uncertainty

Lack of appropriate end points

Studies used FEV1 as primary outcome, but SMC stated that this outcome is known to be a poor corollary with severity of symptoms. Symptoms and risk of exacerbations would have been more appropriate, and these patient-relevant outcomes are recommended by the EMA.

Clinically significant vs. statistically significant results

The results for the outcome moderate/severe exacerbations were statistically significant, but did not reach a clinically meaningful annual reduction. FEV1 results did not reach clinical significance according to EMA guidelines.

Study population issues

SMC noted that two submissions lacked efficacy data in patients with mild or severe disease, which limits generalizability of the studies. Also, SMC noted the exclusion criteria in the trials. For example, one trial only included those patients who were adherent to inhaled treatment, and another trial excluded those patients with certain cardiovascular issues. These populations will likely differ from those in clinical practice so generalizability of findings are uncertain.

Short-term efficacy data

SMC commented on the short-term studies and noted that long-term efficacy data is lacking.

Inappropriate comparators

SMC's most consistent issue with the COPD submissions was the lack of a direct active comparator; this was mentioned in 70% of assessments. SMC also noted that in one submission, the drug was compared to an active monotherapy, but this was not considered a relevant comparator to dual LABA/LAMA treatment.

No evidence in treatment pathway or with combination therapies

Concomitant medication use during one clinical trial did not reflect clinical practice in Scotland.

HAS (France) 

HAS reviewed six drugs/indications. Of these, three were "Do not recommend," two were "Recommend," and one was "Recommend with restrictions."

COPD drugs approved 2010 - 2015; agency decision and areas of clinical uncertainty

Lack of appropriate end points

HAS noted in two assessments that patient-relevant outcomes such as hospitalizations and exacerbations were not included.

Study population issues

Patients with certain cardiovascular issues were excluded, possibly reducing generalizability.

Short-term efficacy data

Studies presented were short term, which lead to uncertainty of long-term effectiveness and uncertainty about adverse events.

Inappropriate comparators

Non-inferiority compared to another LABA was not demonstrated in a clinical study with a direct comparison and sufficient duration.

No evidence in treatment pathway or with combination therapies

Uncertainty about the transferability of clinical results to real-life. For example, one assessment poorly defined the place of the drug in the treatment pathway.

NICE (UK) 

NICE reviewed only one drug/indication and recommended it for research purposes only.

COPD drugs approved 2010 - 2015; agency decision and areas of clinical uncertainty

Clinically significant vs. statistically significant results

Clinically meaningful effect on health-related quality of life was not demonstrated.

Inappropriate comparators

Lack of comparison with an active treatment.

No evidence in treatment pathway or with combination therapies

NICE noted that no direct evidence was submitted for the position of the drug in the treatment pathway.

Note: NICE only reviewed one COPD drug during the 2010-2015 time frame, thus, these observations are based on only one assessment.

G-BA (Germany) 

G-BA reviewed eight drugs/indications; two reviews were conducted in 2015 and have not yet been translated, and the remaining six were "Recommend with restrictions."

COPD drugs approved 2010 - 2015; agency decision and areas of clinical uncertainty

Short-term efficacy data

Studies were short term, thus long-term efficacy is unknown.

Inappropriate comparators

In the majority of G-BA COPD assessments, the manufacturer did not comply with the G-BA-determined appropriate comparator therapy; thus, there was no evidence to evaluate. Because G-BA does not accept indirect comparisons, they were unable to determine the presence of an additional benefit for four drugs/indications.

IQWiG (Germany) 

IQWiG reviewed nine drugs/indications with no binding decision or recommendation.

COPD drugs approved 2010 - 2015; agency decision and areas of clinical uncertainty

Lack of appropriate end points

Mortality/morbidity was not assessed in one assessment. Results were only available for two outcomes so benefits and harms could not be balanced.

Short-term efficacy data

Studies were short term, thus long-term efficacy is unknown.

Study population issues

In one assessment, the manufacturer did not submit relevant evidence for the subpopulation in the indication. In another assessment, there was uncertainty in the classification of patients in the clinical trials, so IQWiG could not determine if the population in the study matched the indication under review.

Inappropriate comparators

Company did not comply with appropriate comparator therapy in three assessments.

PBAC (Australia) 

PBAC reviewed 13 drugs/indications; 10 of those were "Recommend with restrictions" and three were "Do not recommend."

COPD drugs approved 2010 - 2015; agency decision and areas of clinical uncertainty

Lack of appropriate end points

PBAC noted that patient-relevant outcomes such as exacerbations and hospitalizations were not included in two assessments.

Clinically significant vs. statistically significant results

PBAC noted that in multiple assessments, the end point FEV1 demonstrated statistically significant results, but not clinically meaningful results.

Study population issues

Pivotal trial excluded patients with upper respiratory infections and recent COPD exacerbations, resulting in an incomparable patient population. There was possible heterogeneity due to the characteristics of study populations in one assessment.

Short-term efficacy data

Some of the studies were short term and there was limited long-term safety data.

Inappropriate comparators

According to PBAC, inappropriate comparators were used in multiple assessments.

No evidence in treatment pathway or with combination therapies

There was insufficient or no evidence to demonstrate a significant incremental benefit of combination therapy over monotherapy in one assessment. In another assessment, the drug was only assessed as monotherapy, though it is likely taken concomitantly with other drugs, and so, there was a lack of efficacy data in combination with other drugs.

CADTH (Canada) 

CADTH reviewed eight drugs/indications; six of these were "Recommend with restrictions," one was "Recommend," and one was "Do not recommend."

COPD drugs approved 2010 - 2015; agency decision and areas of clinical uncertainty

Lack of appropriate end points

In two assessments, CADTH noted that mortality/morbidity was not assessed, or studies were not powered to assess these end points. In another assessment, CADTH noted that patient-relevant outcomes such as QoL and ADLs were not included.

Clinically significant vs. statistically significant results

In multiple assessments, the change measured for the outcome FEV1 was statistically significant, but the results were of uncertain clinical significance.

Study population issues

CADTH noted uncertainty in the generalizability of the patient population in five assessments. CADTH noted the following: one assessment included a younger population and more smokers than the Canadian population. Two studies excluded patients with certain cardiovascular issues. One assessment's patient population was incompatible with the indication sought, and another assessment had reduced validity due to the high rate of withdrawals and protocol violations.

Short-term efficacy data

In one assessment, studies presented were short-term and could not assess the impact of seasonality, which is important in Canada. In another assessment, studies were too short to draw conclusions about the comparative risk of pneumonia.

Inappropriate comparators

There was no direct blinded data comparing drug to active comparator in one assessment, and drug combinations were not used as comparator in another assessment.

No evidence in treatment pathway or with combination therapies

Studies did not assess the effects of other drugs likely to be taken concomitantly. Studies did not include triple therapy arm.

Real-World Evidence to Fill the Gaps

Areas Where Real-World Evidence Can Reduce Clinical Uncertainty

Safety

The safety of the COPD drugs assessed was a concern of the regulatory agencies. Pragmatic clinical trials (PCTs) with a longer duration and less restrictive patient population can evaluate safety in "real-world" clinical practice.

Lack of appropriate end points

PCTs can focus less on surrogate end points and include more patient-relevant end points to demonstrate effectiveness of the drug from the patient's perspective, which would benefit both the regulatory and HTA agencies.

Study population issues

PCTs have the flexibility to include all patients with COPD, thus including patients previously excluded from most RCTs (i.e., patients with multiple co-morbidities and/or severe disease). These "real-world" populations can improve generalizability to real-world patient groups and provide evidence for the subpopulations relevant for the HTA evaluations.

Study Duration

PCTs can be longer than traditional clinical trials, and thus, can evaluate the long-term effectiveness and safety of COPD drugs. Since COPD is a chronic condition, the uncertainty in long-term effects is a significant concern. Reducing this uncertainty would benefit both the regulatory (specifically the EMA) and HTA agencies.

Comparators

In PCTs, multiple comparators can be used and can be useful for HTAs that request a wide range of comparator therapies to comply with their country's standards of care.

Lack of evidence in treatment pathways and in combination therapies

Within PCTs, practitioners are less constricted on how to apply the treatment, thus evidence can be generated in a wide range of standards of care (i.e., treatment pathways and combinations) that are relevant to HTA agencies.

Use of Pragmatic Clinical Trials in Health Technology Assessments (HTAs)

Have pragmatic clinical trials been used in previous HTA submissions? If so, what is the acceptability of these trials across different HTA agencies?

Methods

To determine how often, and in what manner, pragmatic clinical trials are used in HTAs, Context Matters searched across their data model, which contains 3,590 HTAs from nine HTA agencies[1], for the term "pragmatic." From those assessments that used the term "pragmatic," Context Matters analyzed the assessments to determine how many used "pragmatic clinical trials." For this project, a pragmatic clinical trial is defined as follows: *Pragmatic trials evaluate effectiveness in real-world conditions (e.g., routine clinical practice) with relatively unselected participants and under flexible conditions.*

We combed the assessments that used "pragmatic clinical trials" to find other terms to search for within the data model. The following terms were used to broaden our search:

Open-label

Real treatment situation/actual treatment situation

Results

Of the 3,590 assessments searched, only 10 assessments (0.3%) included a pragmatic clinical trial.

HTA assessments that included the term "pragmatic"	
Agency	Disease Condition
PBAC (Australia)	Attention Deficit Hyperactivity Disorder – 1 initial assessment, 2 resubmissions
HAS (France)	Schizophrenia – 7 assessments

Attention Deficit Hyperactivity Disorder (ADHD): Methylphenidate Hydrochloride Continuous Release (CR) (PBAC)

The PBAC ADHD assessments were for methylphenidate hydrochloride. There were three total assessments that included a pragmatic clinical trial: one initial assessment and two resubmissions.

[1] CADTH (Canada), G-BA/IQWiG (Germany), HAS (France), HIS (Scotland), NICE (United Kingdom), PBAC (Australia), pCODR (Canada), SMC (Scotland)

In March 2006, methylphenidate hydrochloride CR was first evaluated by PBAC for the treatment of ADHD in children and adolescents aged six - 18 years who required continuous coverage over 12 hrs. PBAC had not previously considered a submission for the CR formulation. The evidence base included three double-blind RCTs comparing methylphenidate hydrochloride CR to placebo and methylphenidate hydrochloride immediate release (IR), and a *pragmatic randomized open-label trial* comparing the CR to IR over an eight-week period. The study had two arms: CR formulation given once a day, and IR formulation given three times a day.

The pragmatic randomized open-label trial indicated a statistically significant difference in the proportion of patients achieving remission on the CR formulation compared to the IR formulation. In contrast, the three RCTs did not show a statistical difference between CR and IR formulations in the inattention/over-activity subscale. PBAC was uncertain whether the results of the pragmatic trial were due to real differences in the adherence to and efficacy of the drug or just due to trial design and observer bias. Since the IR formulation was given three times daily and the CR formulation once daily, PBAC suggested that the pragmatic trial could have reduced bias by including a third arm, that would parallel the dosage in the control arm (i.e., three dosages/day of 2 placebo dosages plus once-daily CR formulation). The third arm could have reduced observer bias in the measurement of the subjective outcomes.

PBAC accepted that a once-daily formulation would likely improve compliance, but PBAC could not accept the extent of the benefit (i.e., greater efficacy) based on the results of the pragmatic trial alone. The PBAC thus rejected the submission due to uncertainty in the clinical benefit, which also led to uncertain cost-effectiveness.

In July 2006 and November 2006, PBAC reassessed the drug, based on a new economic evaluation only. The same clinical evidence was presented but a different price was proposed. PBAC recommended listing the drug (on the third submission and after a second drop in price) and stated that, even though the clinical benefit of CR over IR remained uncertain, there were likely improvements in compliance and ease-of-use and this, with the new price, justified listing the drug.

Schizophrenia: Second-Generation Oral Antipsychotics (HAS)

The HAS assessment was a multiple-technology assessment of six, second-generation, oral antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, and risperidone), assessed for two indications each to reassess the efficacy and safety of these products. HAS reassesses drugs at least every five years and, thus, these reassessments were after initial market authorization. Three pragmatic studies were used in seven assessments of these drugs.

The three pragmatic clinical trials compared the effects of second-generation antipsychotics (SGAs) and first- generation antipsychotics (FGAs) in actual treatment situations. The pragmatic clinical

trials showed that, in general, there was no difference between the SGAs and FGAs in efficacy. There were small differences between antipsychotics in discontinuation and safety.

Based on the RCT, pragmatic clinical, pharmacovigilance, and meta-analysis data, HAS determined that there were no real differences between SGAs and FGAs, or between drugs in the SGA class. HAS did not comment on which evidence sources were more influential in their final conclusion.

HTA Calls for Pragmatic Clinical Trials

The terms "real treatment situation" and "actual treatment situation" have been used in three assessments. In all three cases, HAS was calling for a study to document the effects of the drug in the real world. HAS's request for "real treatment situation" data was post-market authorization. HAS recommended all three of these drugs for reimbursement, thus the "real treatment situation" data requested by HAS would be evaluated at the five-year reassessment of improvement in actual benefit. If the additional data was not provided the drug risks receiving a lower/worse improvement in actual benefit score.

HAS requests for data on "real treatment situations"	
Drug (Disease Condition)	Notes
Ranibizumab (Age-related Macular Degeneration [AMD])	HAS requested a study in AMD to document, in actual treatment situations, the conditions for starting treatment, conditions of use (especially dosages), impact of treatment on medium-/long-term change in visual acuity and quality of life, and impact of drug on safety.
Olanzapine (Schizophrenia)	HAS requested a study to document, in a real treatment situation, the characteristics of patients treated, characteristics of prescribers, the methods for prescribing (e.g., dosage, duration of care, withdrawals), and a description of the post-injection syndrome.
Infliximab (Ulcerative Colitis)	HAS requested long-term follow-up information to document the characteristics of patients treated, the conditions for use (especially conditions for initiation of treatment), maintenance of medium- and long-term effects, and long-term safety.

"Open-label" was used in 202 HTA assessments. "Open-label" trials are not necessarily "pragmatic clinical studies," so there will be a large number of false positives in these 202 assessments. The prevalence in use of "pragmatic clinical trials" in this analysis is likely to be an underestimate, but it is unlikely that it is a significant underestimate.

Conclusions

- HTAs do not often assess pragmatic clinical trials. Within the Context Matters' data model (3,590 assessments that met the inclusion criteria), only 0.3% of assessments evaluated a pragmatic clinical trial.
- There are two case studies where pragmatic clinical trials were used. In both of these instances, the pragmatic clinical trials were post-marketing trials.
    - PBAC evaluated a pragmatic clinical trial, whose results were in contention with the RCTs that were also evaluated. This is likely to be an issue when relative adherence to treatment arms differs in the pragmatic clinical trial compared to the RCT. PBAC found it challenging to "trust" the results of an open-label trial that was subject to bias.
    - HAS's reevaluation of SGAs used pragmatic clinical trials. HAS seemed to accept the evidence base (which also included RCTs, pharmacovigilance, and meta-analysis data), but it is unknown how much influence the pragmatic trials had on the overall conclusion.
- Three HAS assessments called for a pragmatic clinical trial to demonstrate the drugs' efficacy in the real world. These three trials were to be post-marketing trials.

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