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April 2014

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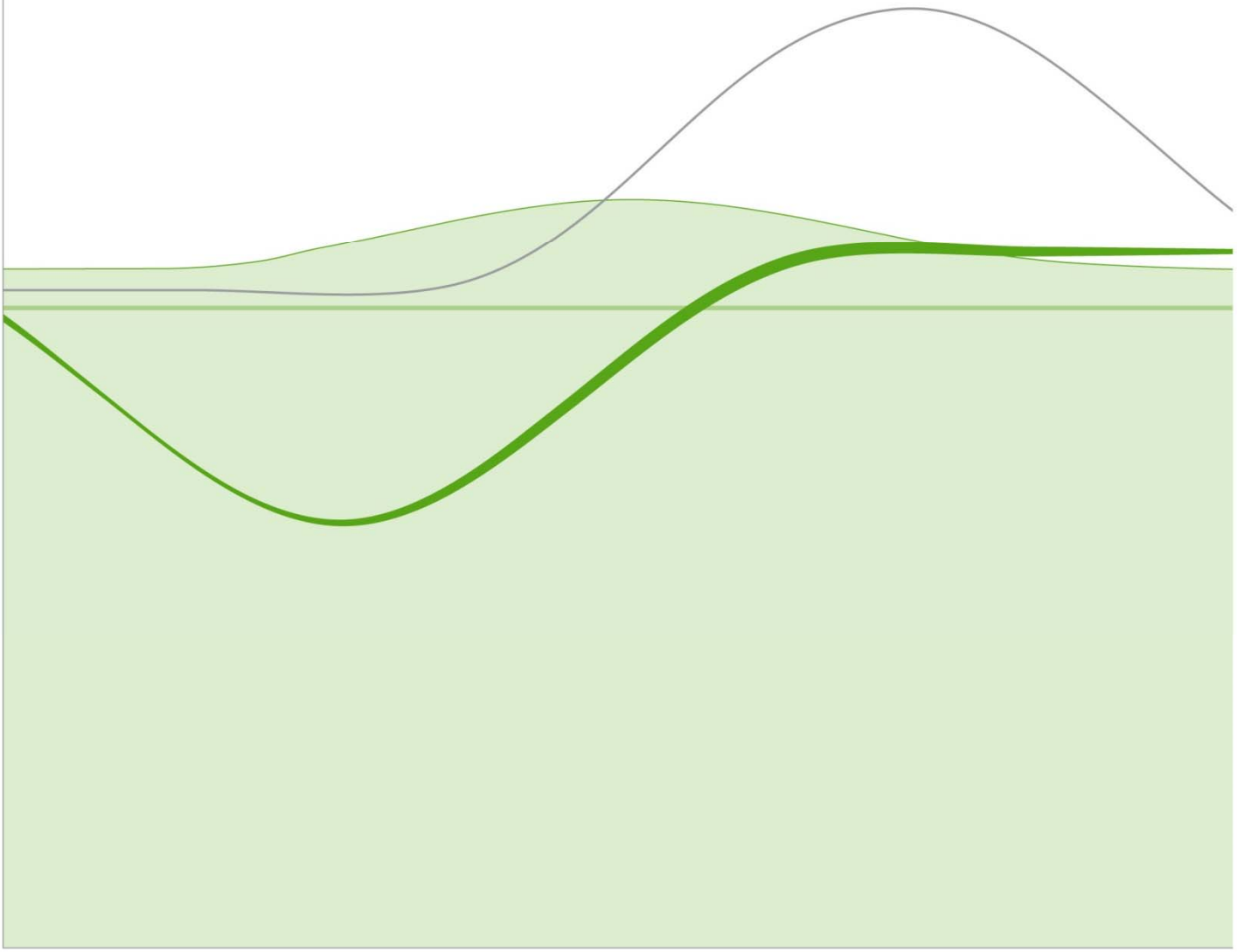

The Current Drug Development Paradigm: Responding to US and European Demands for Evidence of Comparative Effectiveness and Relative Effectiveness

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EXECUTIVE SUMMARY

In the United States (US) and Europe, and indeed, globally, pharmaceutical companies are facing rapidly evolving regulatory and reimbursement evidentiary expectations linked in large part to the clinical and economic realities confronting their respective healthcare systems. Specifically, demands for comparative effectiveness research (CER) and relative effectiveness (RE) evidence have been driven by: (1) health care spending pressures; (2) lack of information to guide the efficient use of new technologies; and (3) consequent political momentum to promote enhanced generation of evidence to inform post-regulatory clinical and coverage decision-making. CER (the term commonly used in the US) and RE (the term commonly used in Europe) both share a focus of producing evidence about how treatments work compared with existing alternatives under circumstances of usual care.

The purpose of this work has been to ascertain how the current drug development paradigm at five global pharmaceutical companies is evolving in response to perceived demands for evidence of comparative effectiveness and relative effectiveness, in particular, from payers and HTA bodies, but also from clinicians and patients. To accomplish this goal, we first undertook a targeted literature review (primarily to provide context and help to identify some themes for the interview programme), followed by a semi-structured interview program with an international sample of 19 senior executives (12 identified as CER experts and seven as RE experts). These executives hold positions in clinical development; health economics and outcomes research (HEOR); medical affairs; and pricing, access and reimbursement (PAR) across five global pharmaceutical companies. Our goal was to develop more detailed information about how these organisations currently conceptualise CER/RE, how they have begun to modify their internal processes to respond accordingly, and what they perceive to be the enablers and barriers for continued adaptation in response to both internal and external factors confronting the pharmaceutical industry.

Both tasks have revealed a number of common emerging themes regarding both CER and RE, and more importantly, how companies are adapting to this new environment which is elevating the importance of information needs of these post-regulatory decision-makers.

First, the current drug development paradigm has already started to change in response to CER/RE evidence demands from stakeholders. These changes range from inclusion of active comparators in clinical trials, involvement of stakeholders to help define key phase IIb and III study design features, incorporation of PRO measures and earlier planning for phase IV studies. It is also true, however, that some of these changes do not deliver on all the elements of CER/RE, particularly the "under usual circumstances of care" dimension. However, our key informant interviews highlighted the need for industry to improve on current methods for eliciting the patient perspective, as their current conceptualisation of CER/RE tends to be primarily payer-focused.

Second, CER/RE investments are being made at different phases depending on the company. Not surprisingly, however, CER/RE investments currently lag behind the phases of initial evaluations. Such evaluations typically involve project team discussions

with representatives from HEOR and PAR. Issues such as the development of initial product profiles and models of expected product effects on clinical outcomes relative to alternative treatments are discussed. If the investigational compound progresses beyond these initial evaluations (including the requisite safety and early efficacy requirements), then typically the project team leader would advocate for the incremental investments to be made in the clinical development program to support CER/RE data collection. The degree to which they focus on this currently in the US as compared to Europe is less, given that the EU has a longer experience of responding to the demands of national HTA/pricing and reimbursement bodies.

Third, a number of barriers have been identified in terms of incorporating CER/RE considerations into companies' drug development plans. While we spoke to a group of individuals that could be characterised as "early adopters" of CER/RE, they identified a number of existing internal barriers to the successful integration of CER/RE within companies. Barriers included a lack of clear accountability for incorporating CER/RE considerations into development plans, and lack of incentives, as well as the high costs of undertaking such studies. However, some of these costs may be mitigated by increased use of observational studies and electronic health record data. However there will need to be additional investments in the research infrastructure to conduct CER/RE as well as on-going methods development and dialogue to ensure regulatory acceptability for promotion of study results in the US. Another barrier raised was the lack of shared understanding on the development team of the importance of external demands for CER/RE data, together with the lack of confidence amongst scientific staff that today's experts have sufficient methods or adequate data to generate robust/valid data from CER/RE studies.

Fourth, a number of facilitators to the successful integration of CER/RE were identified, including an internal champion, often a very senior member of the company who could provide leadership and support, the ability to attract and retain top talent to lead the CER/RE research effort, and external pressures and drivers for CER/RE.

Fifth, there was universal agreement on the part of our interviewees that by the year 2020, CER/RE would have a much greater role in influencing the process of drug development as compared to today. However the question remains as to whether the industry's incremental investments in CER/RE will have the anticipated positive return on investment in terms of reimbursement and market access.

1 INTRODUCTION

In the United States (US) and Europe, pharmaceutical companies are facing rapidly evolving regulatory and reimbursement evidentiary expectations linked in large part to the clinical and economic realities confronting their respective healthcare systems. Specifically, demands for comparative effectiveness research (CER) and relative effectiveness (RE) have been driven by: (1) health care spending pressures; (2) lack of information to guide the efficient use of new technologies; and (3) consequent political momentum to promote enhanced generation of evidence to inform post-regulatory clinical and coverage decision-making.

For the purposes of our work, we used the Institute of Medicine (IOM, 2009) and the High Level Pharmaceutical Forum (HLPF, 2008[1]) definitions of CER and RE respectively:

- The IOM defines CER as the "conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in 'real-world' settings. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels" (IOM, 2009).

- The HLPF defines RE as "the extent to which an intervention does more good than harm compared to one or more alternative interventions under the usual circumstances of health care practice" (HLPF, 2008). This contrasts with *relative efficacy*, which is a comparison "under ideal circumstances", i.e. "under clinical trial conditions" (Eichler et al., 2011). Others have referred to efficacy as "can it work?" and effectiveness as "does it work?" (Luce et al., 2010). Whether there is an efficacy-effectiveness gap has been discussed over the last couple of years (see, for instance, Eichler et al. (2011) and Towse et al. (submitted)). It is important to bear in mind that discussion when thinking about RE. Indeed, as highlighted in different sections throughout the paper, there is confusion around these two terms, as they are often used interchangeably.

Overall, while there are many interpretations of comparative effectiveness (the term commonly used in the US) and relative effectiveness (the term commonly used in Europe) both share a focus of producing evidence about how treatments work compared with existing alternatives under circumstances of usual care.

The environment for supporting CER in the US has been rapidly evolving, spurred in large part by healthcare reform and the premise that better evidence for decision-makers was a central component of a more rational and equitable health care system. CER gained financial support in the US with the passage of the Affordable Care Act and the creation of the Patient-Centered Outcomes Research Institute (PCORI). PCORI aims to provide information about the best available evidence to help patients and their health care providers make more informed decisions. With its current investment of nearly half

[1] The HLPF was a European high-level ministerial platform for discussion between Member States, EU institutions, industry, health care professionals, patients and insurance funds. It focused its work on three main topics: information to patients on diseases and treatment options; pricing and reimbursement policy and relative effectiveness. For more information please refer to: http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/pharmaceutical-forum/index_en.htm

a billion dollars to date in both infrastructure and methods development, as well as comparative effectiveness studies, PCORI has made a substantial contribution to realising the Institute Of Medicine's goal of a learning health care system where "…clinical decisions will be supported by accurate, timely, and up-to-date clinical information and will reflect the best available evidence" (Olsen et al., 2011).

Similarly in Europe, in 2008 the European Commission's High Level Pharmaceutical Forum described the need for greater use of evidence of relative effectiveness to inform decision-making regarding the value of pharmaceuticals. Subsequently, the European Medicines Agency (EMA), the European Network for Health Technology Assessment (EUnetHTA) and others have promoted discussion of both; (a) the potential for evidence of the relative effectiveness of pharmaceuticals to better inform both HTA and post-launch benefit-risk assessment; and (b) practical ways in which evidence of relative effectiveness can be generated and assessed.

It is also important to note that there are some related concepts to CER and RE that have been influencing both policy discussions and drug development for at least the last two decades. These include health economics and outcomes research (HEOR), health technology assessment (HTA), cost effectiveness analysis (CEA) and demonstration of 'value for money' (see Appendix 3 – Glossary). All of these evaluations typically include an evaluation of the impact of a new drug on both health outcomes and costs, from either the payer or societal perspective, although the scope of the analysis may vary quite widely. Against this backdrop, the concepts of CER and RE have been introduced within the past five to 10 years. Therefore, any developments around CER and RE need to consider the aforementioned health economics-related concepts. These trends were addressed in our interviews.

CER and RE do not include the explicit assessment of economic outcomes, but they are nevertheless an important element in any cost-effectiveness/health economics analysis as they provide the 'effectiveness' element of cost-effectiveness. In addition, many of the methodologies for the various types of studies are overlapping, as are the professional backgrounds of individuals who work in these fields. However, an important distinction is that the working definitions of CER and RE we used are based on the original sources (IOM and HLPF respectively) and do not refer to the economic impact of the interventions under study. In the US, CER studies funded by PCORI focus on clinical comparative effectiveness only and explicitly exclude an evaluation of costs. Moreover, the proposition of using cost-effectiveness data more widely in health care in the US has faced long-standing opposition from various quarters, including product manufacturers, providers, patients, insurers and health care professionals concerned that its use may adversely affect access to health care, revenue streams, or R&D investment. Nevertheless, some US insurance plans reflect implicit measures of cost-effectiveness through their co-payment tiering, with higher co-payments for interventions that are less cost-effective (Chambers, 2014).

An important driver for the new environment is the desire of key stakeholders' for manufacturers to demonstrate the relative value of their medicines, which typically requires comparative effectiveness data. A number of emerging pharmaceutical markets may soon follow these trends in the US and Europe. Although pharmaceutical companies

have been adapting to meet these requirements—initially from health technology assessment (HTA) bodies and payers, but now extending more broadly—uncertainty about this changing landscape increases the regulatory and reimbursement uncertainty, impacting the economic risks and costs of drug development.

While it is clear that the current drug development paradigm (CDDP) will continue to change in response to decision-maker information needs, careful analysis is required to predict what shape the new process should take. For example, at what point should companies plan to incorporate more pragmatic approaches to the design of clinical trials, such as inclusion of active comparisons, recruitment of broader populations and usual care settings? How much of this can be done pre-launch? Would greater post-launch emphasis on observational study designs using data from patient registries, data from electronic health records and administrative data be well received by these decision makers? Specifically with respect to the US, how can pharmaceutical companies best leverage increased US federal investment in clinical and observational research infrastructure and methods? Will federal investment supplant, threaten, or complement current evidence generation investments by industry? What types of barriers and enablers will the industry face when attempting to implement these changes? Given the global nature of drug development, how will the industry best adapt to national or regional requirements for additional evidence of comparative effectiveness?

Responding to all the questions raised above is not straightforward and requires a shared conceptualisation of the most likely future scenarios with respect to trends affecting stakeholder demands for CER and RE. This paper summarises the first phase of a broader project specifically aimed at developing alternative scenarios for how the demand for CER in the US and RE in the EU is likely to influence the industry's approach to drug development by the year 2020. The initial component of the project, described in detail in this paper, provides a solid foundation for the broader project, since a key requirement for devising alternative scenarios by 2020 is to first have a thorough understanding of the existing drug development process. This required a detailed understanding of the current (2010-2012) drug development process as reflected by the perspectives of senior executives with extensive experience in drug development, health economics and outcomes research (HEOR), pricing, access and reimbursement (PAR) and medical affairs at five global pharmaceutical companies. The industry has been adapting their internal processes for several decades in response to marketplace demands for evidence of the value of pharmaceuticals.

The objective was to describe how the changing CER/RE environment is currently affecting the drug development process from the earliest decisions to take a new compound into human trials to clinical integration, including how companies are accommodating changing evidentiary requirements for obtaining registration for FDA/EMA approval while also planning for successfully addressing specific payer requirements for pricing and reimbursement. We also explore what they believe are the main drivers for this changing environment.

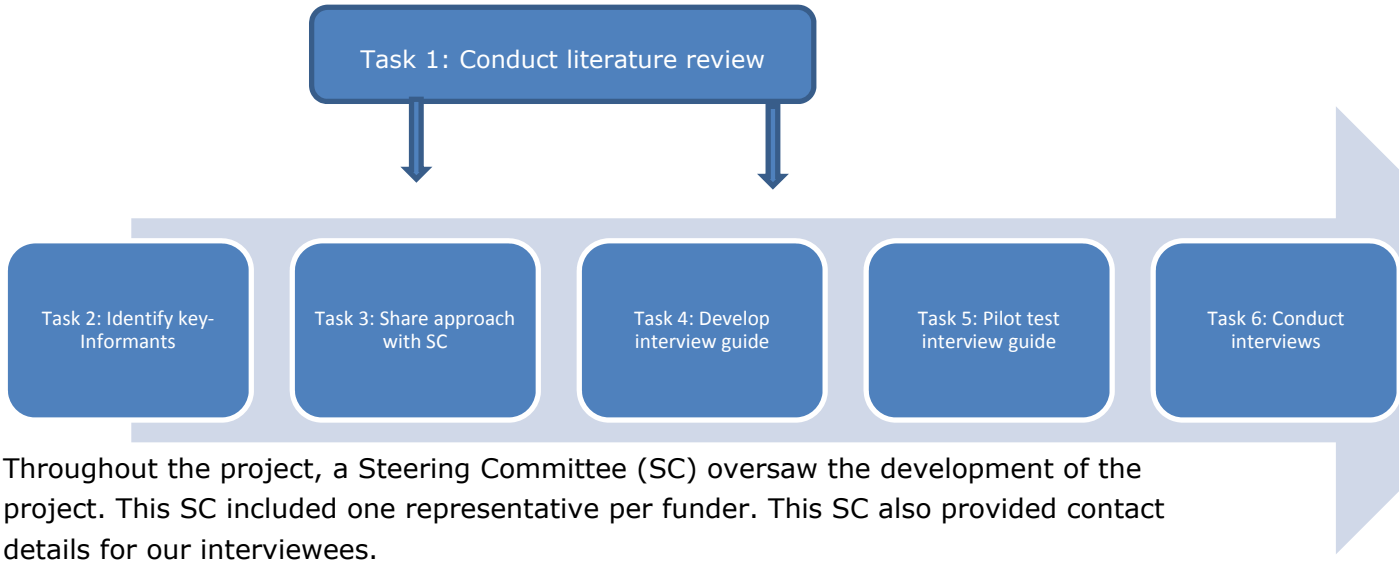
The structure of this paper is as follows: Section 2 describes the methodology used for our literature review and interview programme with pharmaceutical industry informants. Section 3 provides the current context of drug development in which the study was

performed, based on a (targeted) literature review and our previous knowledge. This section also identifies some changes that are taking place already around drug development, some of which are not directly related to CER/RE. However, we feel they are important points to take into account, as these are also having an impact on the CDDP. Section 4 discusses our main findings from the key informant interviews; Section 5 offers a general discussion about our findings, pulling together some key themes. Section 6 provides study conclusions. Appendix 1includes a description of our methodology to filter and identify the relevant papers. Appendix 2 includes a copy of the qualitative interview guide used to conduct the key informant interviews. Appendix 3 has a Glossary of key terms used throughout this paper.

2 METHODOLOGY

For the purposes of this work, we followed a step-wise approach, as shown in Figure 1. The next subsections describe the different steps in greater detail.

Figure 1. Methodology Overview.



Throughout the project, a Steering Committee (SC) oversaw the development of the project. This SC included one representative per funder. This SC also provided contact details for our interviewees.

The main sources of evidence used for this paper were a (targeted) literature review and interview program with industry informants, conducted in this order:

1. Literature review;
2. Identification of key industry informants;
3. Development of pilot test and validation of the interview guide;
4. Key informant interviews; and
5. Combination of literature review and interview data.

We now describe in greater detail the methodology used for the two key activities: literature review and interview program.

2.1 Literature review

Our literature review was not the primary element of this work, and was only conducted to provide context and help to identify some themes for the interview programme. Thus, the objectives were:

1. Assess how CER/RE evidence requirements have been described as likely to impact the CDDP; and
2. Inform and guide the development of the semi-structured interview guide for the qualitative interviews with industry experts.

To identify published literature relevant to this review, we used the search terms "Comparative Effectiveness Research + Drug Development" and "Relative Effectiveness + Drug Development".[2] Appendix 1 has a more detailed account of our methodology.

Our methodology for the literature review is restricted in two ways: time period and key search terms. First, we are aware of older papers that discuss how the drug development paradigm might have been changing since the 1990s in response to demands for evidence of value from payers. However, given our focus was on the effects of CER/RE on the current paradigm, we restricted our literature to 2005 onwards to study this development specifically. Second, other terms such as Evidence-based medicine (EBM), HTA and CEA are often used in practice interchangeably with CER and RE and we sought to minimise the overlap. Luce et al. (2010) provide a useful framework to clarify the typology, nomenclature and interrelationships of the terms EBM, HTA and CER. Plus, as mentioned before, CER and RE fall short of cost considerations.

2.2 Qualitative interviews

Interview Guide

We developed a semi-structured interview guide based on a review of the literature, prior experience and our task objective to characterise the CDDP across the five sponsoring companies from the perspectives of both drug development and commercialisation. The guide was divided into four main sections:

1. Working definitions of CER/RE and distinguishing features as perceived by company representatives;
2. How pharmaceutical companies have already adapted or are currently adapting their CDDPs to stakeholder evidence requirements and information needs;
3. Possible factors that may facilitate or hinder the process of adapting the CDDP to external demands for additional CER/RE evidence; and
4. Opinion of the future direction (next five to seven years) of the CDDP given the changes in external evidentiary demands.

The guide was also customised to focus specifically on CER or RE, given the specific job title, content expertise and location of each key informant. We pilot tested the interview guide with two former pharmaceutical industry outcomes researchers (one in the US and one in the UK) for question order and clarity. This resulted in refinement and reordering of several questions, but did not lead to any substantive changes to the guide. A customised version of the guide was sent in advance to all interviewees (see Appendix 2 for the CER-specific guide). The distinction between having two questionnaires, one for CER and one for RE, was based on the assumption that given their company roles, US-based interviewees were primarily responsible for meeting CER requirements and those outside the US had similar responsibilities with respect to RE. However, as several key informants held global positions, this distinction was sometimes blurred. Therefore, the

[2] Three papers were identified and used from the two different keyword searches.

key questions were identical irrespective of the whether CER or RE was used to frame the topic-specific questions.

Throughout the interviews (and this paper) we use the terms HTA bodies and payers interchangeably. It can be the case that HTA bodies refer to agencies that do health technology assessments, but actually make no reimbursement (appraisal) decisions. But it can also be the case that payers/reimbursement authorities use HTA to make decisions or provide formal guidance. We usually refer to both these possibilities when we refer to HTA bodies and payers, unless we explicitly make a distinction between them.

Key Informants

Our goal was to develop a high level understanding of the CDDP at each company by interviewing a relative balance of CER/RE experts from each company (slightly greater emphasis on CER in the overall pool of candidates given the importance of the US market for the pharmaceutical industry). Our selection criteria were that interviewees had to have two or more of the following professional experiences as part of their pharmaceutical industry career:

- Senior executive or department head in clinical development, HEOR or market access/reimbursement;
- Global responsibilities;
- Strategic role in overseeing drug development or commercialisation process; and
- Tactical role in leading project teams responsible for drug development.

Semi-structured Interviews

All interviews were conducted by telephone and lasted between 45-60 minutes. CMTP research staff conducted the CER interviews and OHE research staff conducted the RE interviews. All CER interviewees were based in the US; some of the RE interviewees were based in countries outside the US. Permission was asked to record the interviews for the purposes of creating interview transcripts; permission was granted by all interviewees with one exception (individual refused).

A systematic content analysis was used to extract relevant information from the transcripts. This process is similar to directed content analysis in that the latter technique deploys a theoretical or conceptual framework to be validated or extended (Hsieh and Shannon, 2005). This framework guided the development of the interview plans and also guided the interpretation of the resulting data. Unlike a traditional content analysis, however, in which in-depth coding of the interview material leads to a detailed (often quantitative) accounting of all coded content or themes, here the primary concern was the complete and accurate identification of the responses to questions (explicit content) relevant to the guiding framework. Hence, in this case what was needed was a systematic process for assuring that all relevant explicit and implicit content was captured accurately.

In contemporary qualitative analysis, multiple coders are increasingly employed to bring more than one analytic and interpretive viewpoint to bear on the collected data (MacQueen and Guest, 2008; Fonteyn et al., 2008). Consistent with this approach, for

the content review of interview materials, two readers reviewed each transcript and recorded the key explicit content relevant to the predetermined conceptual framework obtained in response to each question. To provide a fresh perspective in each case, one reader was not involved in conducting the underlying interview. Similar to the way in which the questions in an interview guide can be used to generate a "start list" of codes in traditional content analysis, the reviewers used a pre-prepared response sheet listing the key questions or issues to be addressed and allowing for additional relevant comments to be appended (Miles and Huberman, 1994). To assure consistency and reliability of the results between analysts, a consensus review process analogous to consensus coding was used to resolve discrepancies in the final interpretation of interviewee responses (Harry et al., 2005).

3 CONTEXT FOR A CHANGING R&D AND EVIDENTIARY ENVIRONMENT

The CDDP is undergoing a transformation – drivers of which are mixed and complex. Based on our literature review, we identified four themes which were then used as the basis for our interviews. Some of these themes cover issues broader than just CER and RE evidentiary requirements. However, they serve as useful contextual factors to help understand the changes we are currently observing.

First, R&D costs of successful new medicines (allowing for the costs of drugs that fail to reach the market) have increased over the last four decades. They have risen from $199 million per successful new medicine in the 1970s to $1.9 billion in the 2000s (both in 2011 prices) (Mestre-Ferrandiz et al., 2012). According to the US President's Council of Advisors on Science and Technology, inefficiencies in clinical trials are a major challenge to the US ecosystem for innovative medicines. The largest single component of the R&D budget of the pharmaceutical industry, clinical trials, cost approximately US $30 billion, or 40% of the research and development (R&D) budget of major companies (US President's Council of Advisors on Science and Technology, 2012). A key factor in increasing R&D costs has been lower success rates for clinical development (i.e. Phases I, II and III) — from 1 in 5 in the 1980s to 1 in 10 in the 2000s.

Second, drug companies have traditionally focused their evidentiary development around registration (i.e. FDA and EMA) requirements (Schoonveld, 2011; Depp and Lebowirz, 2007). This is in part due to the regulatory framework for registration, which in the US still relies predominately on stringent placebo controlled trials to obtain precise and reliable efficacy information[3] (Gottlieb, 2011). The US regulatory approval also does not require CER for new drugs (Edwards, 1970; Temple, 2012). This means that active comparative trials are relatively unusual in submissions to the FDA. Still, the inclusion of active control groups appears to be an increasing trend, with some studies estimating that about 50% of the new drugs approved in the US since 2000 had active comparative studies, including anti-infectious medications and anti-neoplastic agents[4], as part of the pivotal data included in the US FDA approval package (Epstein, 2012; Schneeweiss et al., 2011; Gottlieb, 2011).

The legal framework in the EU is more complex than in the US (Eichler et al., 2010). Current legislation provides for the EMA to request companies to conduct active comparator studies: "In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified" (EC, 2003).

Third, the decision-making power of public and private payers has grown and payers in rich and emerging economies are becoming interested in evidence of value by using HTA

[3] Noting that there are life threatening diseases like cancer where placebo controlled trials are unethical.
[4] This surprisingly high frequency of comparative studies may reflect primarily cancer trials, where it is very common to do trials for (new drug + chemotherapy) vs. chemotherapy alone. But the analysis referred to does not show frequency of comparative trials excluding oncologics. It is also worth mentioning that it would be unethical in many conditions to randomise patients to placebo alone.

evidence to inform healthcare resource allocation decisions (Chalkidou, 2010; Luce et al., 2011). This growth of payer power has been at the expense of individual physicians, as prescribing decisions are becoming more restricted by payers' reimbursement decisions (Eichler et al., 2010). This increased focus on 'value for money' is not a new phenomenon, especially in Europe where cost-effectiveness analysis to drive national pricing and reimbursement decisions has been used over the last 10-15 years. This trend has increasingly begun impacting the CDDP more and more in terms of the evidence companies need to generate during the R&D process (pre- and/or post- launch) to gain and maintain market access for their new products. This evidence increasingly focuses on the 'relative' information versus active comparators (and not just against placebos).

This change is also driven towards more 'real world' information i.e. that the added benefit of a new medicine can be achieved in routine clinical use of the product as well as in controlled experimental conditions. It is worth noting that 'real world' evidence pre-launch is currently not common and tends to be collected, where possible, in post-launch studies. Two factors highlight the increasing importance of "real world" information. First, there is a closer benefit-risk monitoring by regulators over a medicines' life cycle. In Europe, for instance, the EMA Roadmap vision and the introduction of the new pharmacovigilance legislation (implemented from July 2012) allow the regulatory agency to assess how a new drug performs in clinical practice. This facilitates a closer monitoring of the benefit of a medicine as well as its risks, throughout its life cycle. Second, requests from HTA bodies include additional post-launch studies collecting real world evidence.

Fourth, there is a disconnect between what regulators and payers/HTA bodies expect to see in terms of evidence to meet their information needs. For instance, on what constitutes appropriate comparators and whether surrogate endpoints are valid markers of efficacy (Garattini and Bertele, 2009; Shah et al., 2013). Non-inferiority trials for marketing authorisation application will not give payers evidence that the medicine under evaluation is more effective than alternative relevant treatment options, so payers will usually reject them (Schoonveld, 2011, Shah et al., 2013; van Luijn et al., 2008) – or at least payers will not grant the new drug a price premium over the comparator drug on the basis of non-inferiority evidence. This, however, does not mean that payers may necessarily reject reimbursement of the new drug. For instance, in the German AMNOG system, if a new drug shows no incremental benefit, it can still be reimbursed but at the reference price of the comparator. This issue is picked up below when the interviews are summarised, where the importance of CER/RE according to degree of existing competition is discussed. The disconnect is driven in part by the different remit of regulators and payers/HTA bodies; HTA bodies are asking a slightly different question from that the regulator has asked. The EMA explicitly acknowledges this potential disconnect: "In contrast to the benefit-risk assessment carried out by regulators, HTA bodies compare the relative effectiveness of medicines and take their financial cost into account. This can lead to differences in the types of studies needed to support the assessment carried out by regulators and HTA bodies." The European Commission gave the political mandate to the EMA to start interacting with HTA bodies in October 2008 (EMA, 2011a).

In addition, there might be differences in evidentiary needs across different payers. For instance, the comparator in a multi-national trial may represent standard therapy in some European countries but not in others. Other differences include the systematic use, or not, of cost-effectiveness analysis and treatment of surrogate measures (Shah et al., 2013).

It is beyond the scope of this paper to review payer and HTA evidentiary requirements. However, two points are worth mentioning to provide further context. First, methods used by countries to identify, include and analyse RCTs to assess relative efficacy are not similar. Also, the use made of a relative efficacy assessment seems to be quite different across countries – especially to determine access to medicines (Mestre-Ferrandiz et al., 2010). Second, several transformations from (relative) efficacy to relative effectiveness can occur prior to launch– and there are important differences across countries. As pointed out by Kleijnen et al., (2012), "*Although most countries are interested in the relative effectiveness, effectiveness data are often not available around the time of market authorisation of a new pharmaceutical. Our data show that in such cases some countries limit their assessment to relative efficacy. The majority of the jurisdictions, however, sometimes or always attempt to extrapolate effectiveness data from randomised controlled trials to daily clinical practice. In some countries, they refer to a qualitative extrapolation, which is an interpretation (estimate) of the effectiveness of a treatment based on the efficacy data that are available. Some jurisdictions use modeling exercises to extrapolate efficacy data. This does not seem to be common practice in the majority of European jurisdictions and is probably mostly done in countries in which modeling is carried out for a cost-effectiveness or cost-utility assessment*" (page 958).

As a final remark, which results from the third and fourth factor above, there will nevertheless be challenges faced by firms if they were to try to do their registration trials in the format desired by payers. In particular: (1) the standard of care/comparator at the time trials are initiated may be different from the standard of care at the time of launch; and (2) greater trial size, failure risk and cost of non-inferiority and, *a fortiori*, superiority trial.

4 RESULTS – QUALITATIVE INTERVIEWS

Based on the criteria that we provided to each of the five company representatives, a total of nineteen (19) experts were interviewed. All interviewees have extensive pharmaceutical industry experience, with distribution across clinical development, HEOR, medical affairs and PAR (see Table 1). We have classified 12 of these interviewees as experts in CER and seven as experts in RE given their current professional responsibilities. In addition, to safeguard confidentiality, we have grouped the interviewees into four broad departments (percentage shows the relative numbers): HEOR (42%); clinical development (31%); clinical strategy (11%); medical affairs (11%); and PAR (5%).

Table 1. Summary of interviewees' positions

Company	Department*	CER or RE Informant
A	Clinical Development	CER
A	HEOR	CER
A	HEOR	RE
B	Clinical Development	CER
B	Clinical Development	CER
B	Clinical Strategy	CER
B	HEOR	CER
B	HEOR	RE
C	Clinical Development	CER
C	HEOR	CER
C	PAR	RE
C	Medical Affairs	RE
D	Clinical Development	CER
D	Medical Affairs	CER
D	HEOR	RE
D	Clinical Strategy	RE
E	HEOR	CER
E	Clinical Development	CER
E	HEOR	RE

*Informants have been in their current roles between 2 months and 8 years.

We report our key findings from the interview programme, based on the four general headings that were used to frame our interview: definitions, current changes, barriers/facilitators and future direction. Within this framework we consider the various ways companies might respond, along the R&D timeline, to the higher evidentiary and cost implications of CER/RE demands.

4.1 Definition and features of CER / RE

4.1.1 Personal definitions of CER and RE

The definition of CER provided by informants was relatively uniform, and generally reflected the Institute of Medicine definition. Most informants stated that CER includes a comparison of the benefits and harms of a new therapy versus the standard of care or another existing therapy in a given patient population. Informants believed that CER encompasses drugs, devices, surgical interventions, prevention measures, diagnostic tools, monitoring devices and varying care delivery methods and health care settings in which care is delivered. They also emphasised the real world setting in which CER studies are performed and the fact that real world evidence and data are incorporated into CER studies. To make his point regarding the fact that CER entails studies that take place outside of a controlled setting, one HEOR informant stated that in comparative effectiveness we need to consider the different kinds of healthcare settings in which a combination of different kinds of interventions are taking place and how they are delivered.

Another informant, from a clinical development team, also emphasised the real-world aspect of CER, stating that CER entails information that is more relevant to providers than studies performed in highly controlled settings. This executive further stated that "I do not include in my definition of CER…head-to-head highly controlled randomised trials. Some people do. I think that…generally speaking those are still trials being conducted with very restricted inclusion and exclusion criteria and eligibility criteria" and this does not encompass CER. The majority of interviewees agreed with this line of thinking in that they clearly distinguish between CER and efficacy trials, with five CER interviewees stating specifically that CER goes beyond comparative efficacy. These informants, from the HEOR, clinical and medical affairs sectors of their organisations, agreed that CER does not encompass head-to-head highly controlled RCTs (typically in phase III) that evaluate a therapy against a comparator. Finally, one medical affairs executive stated that he does not view CER as simply the evaluation of certain outcomes, but as assessing the overall outcome of the population treated with the new therapy versus the overall outcome of the comparison population. He reported that "effectiveness is more than efficacy. It is what the overall outcome is of the treated population relative to the outcome of the treated population with the alternative therapy."

All RE informants generally stated that RE relates to how the technology compares to the alternatives available, including the standard of care, under the usual circumstances of healthcare/clinical practice (i.e. RE is thought of as real world evidence). The alternatives available relate to an active comparator unless a placebo is a real world treatment option. There was some disagreement as to the extent to which RE is intended to inform economic decisions. For instance, one medical affairs executive highlighted that RE is about providing a value proposition for new medicines. Alternatively, an HEOR executive at a different organisation stated that while alternative methods will be used, including indirect comparisons, trial to trial comparisons and statistical techniques, RE "stops short of economics." RE informants were not as clear in their distinction between relative efficacy and relative effectiveness as CER informants had been regarding comparative effectiveness and efficacy. For example, one HEOR interviewee raised the distinction

between RE and relative efficacy – defining the latter as being more about comparative information in pre-launch trials, prior to the real world setting. She argued that "people use these two terms interchangeably, and (the terms) needs some real clarity."

Overall, our CER and RE respondents respectively highlighted very similar characteristics for both terms – in particular, the relative aspect versus active comparators (and not just placebo) and the clinical practice settings. For the RE debate, however, there seems to be more confusion about the differences between effectiveness and efficacy. As one informant stated "If it is still a clinical trial is it possible to actually call this relative effectiveness? I guess it is but it is still not real world per se – it is relative efficacy as opposed to relative effectiveness. Relative efficacy is a first step towards relative effectiveness, where it might be established later in the development process or post-launch." There was general consensus across our respondents that both CER and RE fall short of economics – but with the proviso that some European payers use (to varying degrees) cost-effectiveness as part of their decision making, and relative effectiveness is a key component for this analysis.

4.1.2 What are the differentiation features of CER/RE and why (e.g. as they relate to study design, registration, price and reimbursement)?

One CER informant stated that "it is hard to separate what is CER and what you need to do to demonstrate the value of a medicine." Currently the generation of CER evidence is not a regulatory requirement – and hence, as stated by one informant (and discussed in greater detail below when discussing internal barriers to implementing CER/RE), companies are focused on the evidence needed for registration. However, as stated by this same interviewee, "if comparative effectiveness becomes a regulatory hurdle that will change the way we think about what evidence we need to generate."

Three CER informants mentioned that focusing on the relevant end points was critical, in particular suggesting that these should not only be meaningful from a patient perspective but also should matter to stakeholders other than regulatory authorities.

A number of interviewees discussing CER also raised the challenge of the pragmatic nature of CER – giving rise to the trade-off between achieving greater external validity at the expense of internal validity. As stated by one informant, CER "lends to a very creative and innovative way (of) looking at data … seen by some purists as maybe not as scientifically accurate as the RCT setting. CER is seen by many now as equal to the core type of data we generate from any clinical RCT setting."

In Europe it is important to differentiate between registration and pricing and reimbursement/HTA requirements. In the regulatory space, as stated by one of our RE informants, "Europe is a bit ahead of the US because Europe seems to have been a little faster to embrace the idea of active controlled trials." One informant argued that payers and HTA bodies are driving this move towards active comparators in clinical trials. Moreover, in Europe comparative studies are usually part of pricing and reimbursement /HTA processes – although important differences exist across European countries. Commenting on these differences, two RE informants highlighted that a key issue surrounding RE is ensuring that the different evidence requirements from EU countries are satisfied.

There was consensus across most of our interviewees that one of the key challenges relates to the choice of comparator. CER/RE require head-to-head studies where the current standard of care is the comparator. From the company's perspective, this raises the issue about what comparator to use in phase III trials when the standard of care varies by region or type of patient. More importantly, the comparator used for the regulatory process may not be the one deemed as appropriate by payers/HTA bodies. For example, the company may prefer to conduct a placebo-controlled trial due to the implications for lower sample size and lower trial costs, but this choice will obviously not satisfy the needs of payers/HTA bodies. Yet, when choosing an active comparator, there are limitations regarding the generalisability of this choice across all major markets.

Two RE and two CER interviewees raised having a well-defined patient population as a critical dimension. One CER informant argued that irrespective of whether the trial was carried out before approval or whether it was a CER study, "any good study design requires the engagement of physicians, patients, payers, as well as, regulatory authorities."

4.1.3 Is CER/RE a disruptive or incremental change and why?

At a broad level, most of our interviewees consider the introduction of CER/RE requirements not as a dramatic change, but rather as an evolution in the US and as an expansion in Europe, to denote that the new requirements have been introduced gradually, over at least a 10-year time span. It has been an evolution in the US because the standard of clinical studies is evolving from placebo-controlled trials to head-to-head studies. CER informants stated that "I would not call CER disruptive; it is aligning with the current landscape" and "it is a more modest expansion of existing evidence demands. I would put it on the HEOR trend line." RE interviewees argued that "these changes have been happening over the last ten years. I think the last decade has been really instrumental in bringing this change, but it was not an abrupt change"; "HEOR teams have essentially always been doing it." In this sense, Europe is ahead of the US because in Europe comparative studies have been required for a long time to achieve reimbursement. The current change in the demand of RE evidence in Europe can be considered as an expansion of that trend. It is outside the remit of this paper to explore the different payer agencies requirements – more information can be found in Moloney et al. (sumbitted).

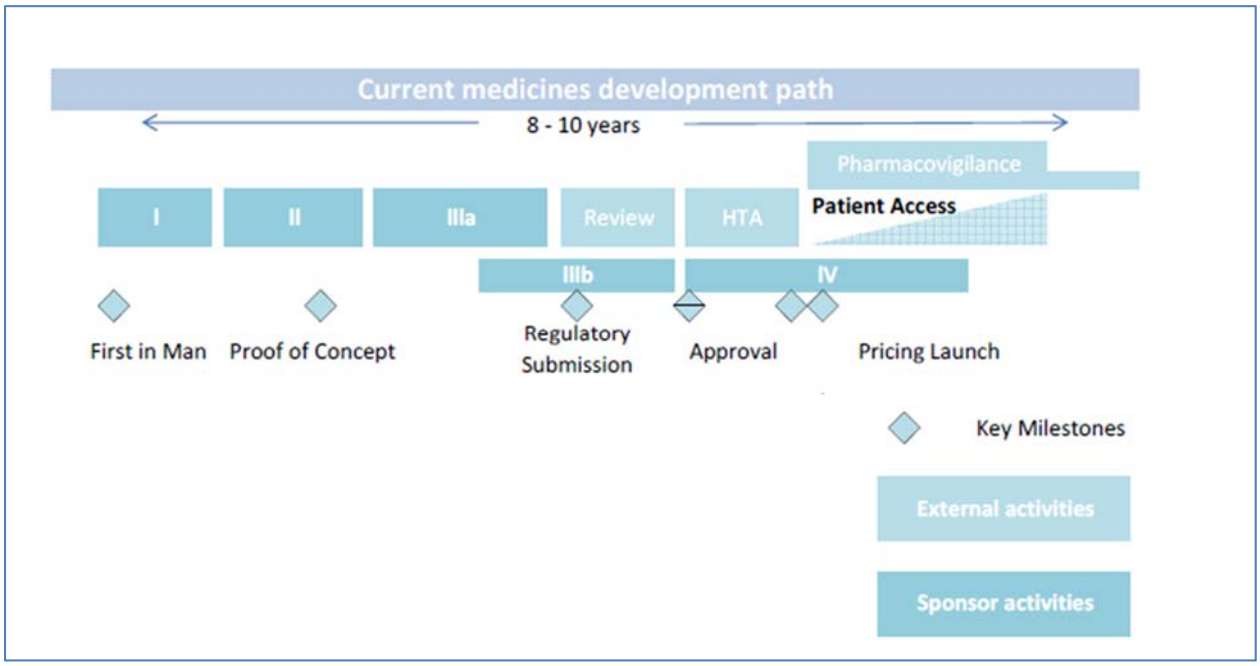
However, a few of our CER interviewees commented on a number of aspects that would be deemed as disruptive. These included the emphasis on evidence generation by payers or if CER ultimately became a requirement for approval. One CER informant even argued that "up until now we have not been doing too much of it (CER)…we have been really focused primarily on delivering the requirements for regulatory approval. So CER needs to be built for the expectations (and data needs)….for payers, providers, patients, and other associations (in addition to regulators). But it is disruptive because it means changing our whole approach to drug development."

Importantly, different companies are at varying points on the evolution, so there are companies that are more confident of operating under the CER/RE requirements than others. The next question addresses some of these changes relative to a high level characterisation of the CDDP.

4.1.4 Does a traditional figure characterise the current CDDP?

We shared Figured 2 with the informants prior to asking this question.

Figure 2.Traditional CDDP Paradigm.



Source: Barker, 2011

The objective of this question was to assess whether Figure 2 was a reasonable portrayal of informants' CDDP. Half of the informants from both the CER and RE interviews stated that the traditional drug development paradigm shown in Figure 2 is, at a high level, a reasonably accurate portrayal of how their organisations conduct drug development. Most provided answers along the lines of "it is pretty much our model," "it looks more or less like the path that we are on right now," and "it is a reasonably close figure to what we do most of the time."

Differences raised by informants between their CDDPs and the figure were generally at a more granular level. Examples of differences raised by informants included proof of concept (POC) being located earlier (at least before phase II), pharmacovigilance constituting an internal activity (and not external) and being considered in phase II but primarily at the beginning of phase III, given submissions to regulatory authorities require a risk management plan (RMP), having distinct phase IIa and IIb trials, and lumping together phases IIIa and IIIb.

A substantial minority did not agree that the diagram was correct. One informant stated "This is the old fashioned sequential drug development paradigm and at our company we have a different approach in a lot of ways." As an example, the informant stated that his organisation conducts parallel POC studies prior to phase I to determine the highest unmet medical needs and then moves forward with one indication, or multiple indications in parallel. A second interviewee argued that the process within his company is more an

"exploratory, confirmatory" process rather than the version in Figure 2 which represents the "old learn and confirm concept."

Many informants also discussed how they are seeking HTA advice earlier in the drug development process and incorporating it into their trial design in earlier phases in order to better derive the evidence that is requested by payers and HTA bodies, and especially to help design phase III trials. Along these lines, one informant felt that the paradigm was outdated in that it did not adequately reflect the degree to which the commercial side has become integrated into development. He stated that "We are thinking about the commercial potential of the medicine earlier since we are reacting to a world in which an increasingly smaller proportion of molecules can be successful enough to merit commercialisation." The exact nature of this interaction is explained below under the question discussing engagement with stakeholders.

It should be noted that most of the informants who generally agreed with Figure 2 also provided examples of how their processes have changed recently. Several informants emphasised that drug development is not as sequential as it has been in the past, with "more done in fluid chunks." Even more apparent were the ways in which organisations are altering their traditional phase II and III processes, often due to the increasing emphasis organisations are placing on CER/RE earlier in the development process – or at least relative efficacy (bearing in mind that as mentioned above, some of the interviewees were using the terms 'relative efficacy' and 'relative effectiveness' interchangeably). This development was discussed by several HEOR informants. For instance, one HEOR executive stated that her company's phase II and III activities are increasingly taking place along a continuum, rather than as distinct phases, with issues related to effectiveness being introduced earlier in phase IIa, and phases IIb and IIIa becoming more blended into one stage. An HEOR executive from another organisation stated that phase II has become incredibly important, with POC being performed in phase IIa and phase IIb being used to inform phase IIIa trial design. He stated that in the past two to three years, phase IIb has become a more important phase for obtaining comparative information and testing endpoints beyond the primary study endpoint. According to this executive, "this is not the case for some areas where you might go into rapid progression if it is a rare disease or an oncology medicine, but for many other areas the importance of a phase IIb trial is that it helps you inform not only dose escalation but endpoints and some early relative efficacy data to inform the phase III trial." Still another HEOR informant, from a third company, described how his R&D considers in phase II whether a molecule will have commercial success whereas five or six years ago they only considered whether the molecule would have a large enough effect as shown in a trial.

Certain informants from the clinical development space also provided examples of recent changes to their development processes. For instance, one clinical development executive echoed the fact that the differentiation between phases II and III is becoming less clear, stating that this is particularly apparent in certain therapeutic areas such as oncology. Similarly, another informant also highlighted how his organisation seeks joint HTA and EMA advice in Europe which is used in phase II to obtain a better understanding of what would be required for reimbursement and hence help plan phase III trials – in a

sense, trying to integrate simultaneously, rather than sequentially (i.e. regulator followed by payer), the views from both stakeholders.

A few informants spoke about how the CDDP has shifted with regards to how patients' views are incorporated into drug development plans. One informant stated that his organisation evaluates the potential for patient reported outcomes (PROs) as early as phase II, due to the FDA rules on using preapproved instruments for evaluating PROs in phase III trials if a PRO label is sought. Another informant specifically stated that while he agreed with the 'Patient Access' triangle in Figure 2 that indicates increasing patient access over time after the 'HTA' box, he would move it earlier in the development process so that it is shown to be "ramping up" throughout the time that HTA is performed, immediately after approval.

4.2 Adapting the CDDP to evidence requirements

4.2.1 At what phase are CER/RE considerations made?

The interviews included two related but distinct questions pertaining to the phases during which CER/RE is being incorporated into the development process. The first question focused on CER/RE considerations, meaning at what point were CER/RE evidence requirements first discussed by the HEOR, clinical and other team members responsible for drug development and factored into portfolio management decisions and drug development plans. The second question focused on CER/RE investments, specifically in which phases of development were financial investments being made towards incorporating CER/RE factors into study designs (e.g. addition of active comparator arms, registry studies, pragmatic trial design features) and other enhancements to the development plans.

Informants provided a range of answers when asked at what stage of drug development is CER/RE first considered, with responses ranging from pre-phase I through phase IV. However, there was a slightly higher number of informants who stated that phase II was the point at which considerations were first made. Additionally, several CER informants expressed regret that their organisations were not considering CER earlier in the drug development process. One such informant stated that "right now, we are thinking about this too late. Now it is happening as we are going into the confirmatory phase for a phase III trial, but it should really be occurring early in phase II." Another CER informant stated that "essentially the thinking process has to come forward to try and generate more of the evidence—if I use that in a payer sense—in phase IIIa than we would have done previously. Previously the drug would have gone on the market and in a few places we might have done some extra work to improve access. Now that is all getting rolled forward." A third CER informant stated "ideally it should happen earlier but in our world the dialogue seems to be happening now at the phase II to IIIa transition point."

CER informants also provided certain insights into why CER considerations are introduced during certain phases and how this informs the overall development process. For instance, one informant stated that CER is considered even before a drug enters clinical development, due to the growing importance for companies to show the potential impact of a medicine both on individual patients and the population. Other informants cited the need to assess what the standard of care will be when the drug finally comes

onto the market and the importance of knowing evidence generation demands on the part of payers and HTA bodies.

RE informants echoed the reasons provided by CER informants for incorporating RE into the development process at phase II or earlier. One stated "I think (planning to incorporate) RE takes place around phase II. Certainly it is in place before the phase III trials need to be planned and if it can be done in phase II that is critical." There was some concern on the part of RE informants as to whether it is possible to conduct relative effectiveness in the context of a clinical trial, and whether relative effectiveness and relative efficacy were one and the same.

4.2.2 At what phase are CER/RE investments being made?

Generally, both CER and RE informants stated that their investments were being made slightly after CER/RE were first considered. Nearly all informants stated that investments were being made at phase II and onward, with most informants reporting that heavy investments were often made in phase III and later. One informant stated "If I look at our current phase III programs the vast majority of them have within those development programs very deliberate comparative data (collection)." One other informant said that "Global health outcomes begins at phase II - understanding what is going to be needed post-launch and in terms of effectiveness versus efficacy…The drug development group is focused on regulatory submission. Thus, phase II is the stage at which health outcomes are considered, but CER investments are being made at stage IV." Another CER informant said that "The big investments are in phase III. We are trying to build into that phase what will be required for access or the types of things that are needed by HTA authorities". Requirements from HTA authorities, however, would go beyond CER and RE – but as mentioned above, RE (or at least relative efficacy) is a key component for any cost-effectiveness analysis.

However, there were a few informants who reported investments being made at a much earlier preclinical stage, while others clearly believed that real CER/RE investments did not happen until the post-approval phase. Informants provided some insight into why investments are often made at later stages than when CER/RE is first considered. For instance, one stated that the investments were weighted based on the stage of development; whereas CER/RE might be considered at earlier stages, it was not until the drug made it to the later stages that actual CER/RE investments were deemed a productive use of resources. Another reported that "one of the key determinants (in making investment decisions) is obviously the risk-benefit profile of the compound. To move it forward toward development we need to know that in fact this is something that has an unmet need."

There was also some disagreement among CER informants regarding whether companies should be making investments earlier in the development process. One CER informant highlighted how CER investments might be moved forwards within his organisation, stating that "Currently, it (CER investment) is almost certainly in the post-marketing arena. That is when we begin to get busy with doing comparative analyses, but I think it is transitioning to where it will be a combination of post-marketing and phase III." On the other hand, another CER informant gave a reason for only investing in "true CER real world evidence" post approval in the US, highlighting the differences with Europe:

"because to do some of those types of programs, you actually need to have the drug approved. So I cannot conduct an observational study for a phase III assay. I have to wait until it gets the marketing approval in the US to be able to do that. Parts of Europe have been able to take a different approach (regarding the possibility of including active comparators in trials before regulatory review). That's not currently the framework that we operate with in the US, though."

4.2.3 Has CER/RE affected go/no-go decisions (i.e. portfolio management decisions)?

Informants in the US expressed a diverse range of opinions on the issue of whether CER considerations have affected go/no-go decision, with half of them reporting that in their experience CER had affected portfolio management decisions. For instance, some companies routinely include CER evidence considerations, such as looking at how the product compares against competitors and how payers might value the product. Companies leverage this information in different ways, such as incorporating it into multi-criteria decision analysis for portfolio prioritisation. One informant even stated that it is crucial that his company better incorporates CER into decision making at an earlier point in the process so that the decision to move forward with a product is based on medical need and then ensuring needed comparators. The other half reported that CER has not been the driver for go/no-go decisions, since the typical reason why candidates have been discontinued is that they did not show a good efficacy profile.

Out of the six RE interviewees who responded to this question, five of them said that RE has affected go/no-go decisions, as RE evidence has been used to inform the value of a drug compared to the competitors or to understand whether the candidate could further be improved to maximise its value in the real world. One of these five informants, however, stated that "RE considerations are not used as much as they would probably want it to be." The remaining informant clarified that RE considerations alone do not drive the go/no-go decision, as this is determined by a combination of factors that can influence the commercial success of a drug, but including relative medical value, which could be thought of as the same concept as RE. Similarly, another informant pointed out that the possibility of achieving commercial success is the main driver of go/no-go decisions; although we believe that RE will be an important factor determining commercial success.

4.2.4 How do CER/RE considerations vary by product type?

The CER/RE definitions used as a starting point for this research do not vary depending on the therapeutic area. Nevertheless, informants agreed that the importance of providing CER/RE evidence does vary across product types, especially when it is necessary to show how a product differentiates from similar medicines in the same therapeutic class. This could be the case of the so-called 'me-too' drugs or medicines targeting a disease where there are many available alternatives. For me-too drugs, especially when there are many cheaper (generic) alternatives, the competition is fiercer and the need to differentiate the new product in order to achieve reimbursement was stated as a clear case for the need for CER/RE data. As one representative from clinical development stated, "But once you get into a more commoditised market, obviously, CER becomes much more important because you have got to show how you stack up in

the real world." It is therefore more necessary to provide CER/RE evidence as part of a reimbursement request – especially if the aim is to achieve a price premium relative the existing competitors.

Providing CER/RE evidence is less necessary for medicines that are true novelties, and that show a good efficacy and safety profile, as the clinical evidence would be stronger in this case and it would be less necessary to differentiate the product from existing therapies. For first in class products, it could even be the case where a standard of care does not exist so comparisons would not be an option. In particular, when first in class products are associated to a validated and specific biomarker, the requirements for CER/RE evidence would be minimal. Still, one informant argued that "I believe CER is less necessary for something that is truly novel, but you still have to demonstrate value. Even if you are in a space without a comparator you still need to show value in order to justify the price of your molecule".

The need to do additional comparative effectiveness research may be minimised for orphan drugs, in particular because there may not be a standard of care, or there is standard of care but there is no agreement about a single standard of care. However, patient associations may demand certain evidence that would be valuable to them so the manufacturer would still be interested in producing CER/RE data, such as PROs.

4.2.5 How are external stakeholder groups consulted?

Informants stated that their companies typically have advisory boards/panels for clinicians and providers – and this has been happening for a long time. Companies typically engage with clinicians to assess their views on the therapeutic value of the drug. Two informants focusing on RE reported that recently engagement with clinicians also focuses on getting their perspective on the relative value of the drug (i.e. the value over the competitors).

Many informants also discussed how they are seeking HTA advice earlier in the drug development process and incorporating it into their trial design in earlier phases in order to better generate the evidence that is requested by payers and HTA bodies. These informants felt that HTA consultation is becoming increasingly embedded in the clinical development path so their organisations know what kind of evidence HTA bodies might require. More specifically, organisations are seeking input on "which product attributes or differentiation elements would be convincing or compelling enough to propose a very impactful value story." In general, organisations reported that they are seeking early scientific advice from HTA bodies prior to phase III so that it can be incorporated into phase III trial design. This scientific advice focuses on choice of the comparator and outcomes measures, for example. Most companies recognise that the interaction with HTA bodies has recently become more important, especially in countries with a strong HTA tradition, as this helps them to identify the potential elements of value in the drug.

Informants who specifically stated that they would relocate the HTA component of the diagram illustrated in Figure 2 above indicated that they generally seek early scientific advice from HTA bodies in phases I or II so that the input can be leveraged when planning phase III trials. One informant also stated that there is considerable overlap between phase III trials and HTA as performed by his organisation, and that they are

performing HTA up to one year before approval in markets such as the UK, Canada and Australia – countries with strong HTA tradition. One informant stated that given recent changes in France and Germany around pricing and reimbursement and the assessment of new medicines, they are now beginning to engage with payers in these countries before approval, at least a year before. How companies engage with HTA bodies and payers also depends on the available infrastructures to do so. Another informant also stated that his organisation uses the joint HTA and EMA advice process early in phase II so as to generate HTA RE data in phase IIIa in support of approval.

Engagement with payers also usually occurs at similar stages as engaging with HTA bodies. Payers are involved at multiple levels (regional, national, global) to assess the reimbursability of the candidate drug. One CER informant even said that engagement with payers in phase II have affected portfolio management decisions. A number of informants mentioned that they sometimes engage with former payers too. One CER informant also stated that there are increasingly engaging with pharmacy groups, such as Walgreens – even to jointly set up an initiative looking at real world evidence within the pharmacy setting.

Patients are involved and consulted only marginally (only four informants in total claimed that their company makes explicit efforts to take into consideration patients' perspectives) and companies tend to engage them as subjects for research only. As an illustration, one informant argued that "I would say that when it comes to incorporating the needs of patients we are less good and we are less clear how to do that effectively." The position of the patient is typically translated through providers and payers. (For instance, in Europe patient representatives are involved in the decision-making process of the regulatory bodies (e.g. EMA)). However, this position is evolving and most companies are starting to include the patient's perspective into the development decisions, although a paradigm to capture their preferences has not been established yet. The same informant as above said, however, that "We currently have an extensive effort towards better engaging the patient". Other informants expressed themselves along the same lines: "We talk a lot about how we can engage patient groups more. I think we are getting better at that but we have still got a long way to go so I think that is a downside for us right now"; "I think it is true that the commercial group often does focus groups with patients but I do not think that we are getting the same degree or quality of input from patient perspectives as I think we should be; it is really needed in the drug development process"; "Patients are actually being included in development process much more nowadays than what I remember before."

For instance, one company reported they are actively interacting with PCORI, while other companies are using multimedia tools. Indeed, as highlighted by one of our informants, "patients' participation is being facilitated by social media, which is an inexpensive way to do this. This enables us to get feedback from patient groups." This same informant argued that patients have also become more empowered and engaged in management of their disease – probably "starting first with the HIV population, and now there are many more patient organisations that are actively trying to engage in the discussion around drug development and therapies". An RE informant also echoed a similar view: "I think a lot of our interaction with patients is of a more general nature. Now for some

places where patient groups are strong, then obviously we will engage with them". But differences across therapeutic areas were also highlighted, in terms of company's activities and its previous knowledge: "If the disease area is new to the company, you will probably have a greater need in finding out what patients are thinking than when you already know so much about the patients that you do not have to specifically do some research for that particular molecule". This issue could also be seen as a response to how drug development is changing in response to the increase demands to demonstrate value and not specifically to CER/RE as defined in this paper.

4.2.5 Are CER/RE-related protocols developed globally or at the country level?

The majority of respondents stated that the answer was not a simple choice between these two alternatives, but rather represented a combination of both options in that CER/RE protocols are developed at both the global and country levels. In general, the clinical development approach tends to be global but a single, global phase III clinical trial does not fit the evidence requirements for all the key markets. Therefore there are groups of experts at country level that advice on which evidence needs to be collected and generate the protocols for the local reimbursement agencies. As stated by one interviewee, "variations in medical practice, in available therapies, and other country-region specific issues means that we often cannot meet the needs of regulators, payers and prescribers everywhere with one study." These groups are usually assigned with their own budgets, depending on the market importance, to conduct their own studies (which need to be consistent with the global development plan). Companies typically have between five and 15 key markets where they ascertain whether local evidence is required.

In terms of the role of transferability of data across different countries, one RE informant discussed the willingness of some European countries to accept evidence from other countries: "The UK has such a rigorous process…that they actually do take into account information from other countries…we believe that the UK feels comfortable to adapt the information from other places for their own purposes, whereas in countries like France, we still get a strong message that they like to see (French) data. In the Commonwealth countries, the ones that have a strong HTA tradition, we think they are further along and more comfortable with extrapolating data."

There are contrasting feelings about the possibility of harmonising the evidence requirements across countries. Some informants believe that we are moving toward a harmonisation of the requirements; others think the opposite and foresee that clinical studies will increasingly be designed to satisfy requirements at local level. The issue of trends in evidence requirements is picked up later in the discussion on the predictions for the future outlook.

4.3 Barriers and facilitators to CER/RE

4.3.1 Internal barriers and facilitators to CER/RE

For key informants focusing on CER that were from drug development, the most frequently mentioned barriers were that it was difficult to understand the full range of evidence requirements across the various markets for the drug and how to incorporate

these into the clinical development plan. Correspondingly, there were the implications for increased study complexity costs and the associated trade-offs that inevitably accompany decisions regarding additional investments in the clinical development program. Some senior executives expressed concern that there is a lack of confidence in both the scientific and regulatory communities that there are either sufficient methods or adequate data to ensure the validity of results from CER studies. These concerns reflect the lack of consensus regarding how to account for the enormous variability in practice styles and patterns that exist in the US, the lack of data standards and interoperability of electronic health records for research applications, as well as the shortage of trained researchers to conduct sophisticated CER studies. One senior clinical development interviewee said that in his organisation, "we have sent a bit of a mixed message internally. On the one hand we are trying to make our clinical trial programmes and their individual studies as lean and simple as possible, but the more CER elements you add to the studies, such as comparator arms, the more complex the studies become. We need to find a way to balance these two needs to address the needs of regulators and also payers and prescribers."

For informants that led outcomes research functions, their perspective was that some of the biggest internal barriers were related to a lack of a shared understanding of the increasing external demands for CER amongst all members of the clinical development team, as well as team members' preferences for traditional RCT data and a general scepticism about the use of real-world data and pragmatic RCT or observational study designs. Pragmatic RCT and observational studies are very different but relate to different dimensions of CER. There were mentions of novel approaches to address these types of concerns, such as using practice-based research networks to conduct "CER trials" that would essentially continue "endlessly" as they would follow patients throughout their enrolment in a practice to document long-term outcomes. Another major concern was the cost of CER studies and the fact that this type of evidence generation will require more investment from companies. Also mentioned by this group was that the decision to pursue CER studies requires risk taking because companies are now studying their drugs in broader patient populations and against active comparators, whereas in the past the drug was studied in clinical trials with much more homogenous study populations, and often with placebo-controls or as an add-on therapy. These informants all stated that these issues were more readily addressed when there was an internal champion, often a very senior member of the company who was able to hold teams accountable for incorporating CER evidence considerations into the development plan and for providing leadership and tangible support to conduct the necessary studies.

Within our RE interviewees, there was only one informant representing clinical development and one from medical affairs, therefore we do not want to overemphasise the differences between their perspectives and those shared by the five interviewees representing the outcomes research perspective. However, these two individuals did state the need for greater predictability and clarity regarding how exactly clinical development programmes will need to be altered to meet the RE evidence requirements, particularly given that different countries often have their own specific requirements regarding comparators and types of analyses required by HTA bodies for pricing and reimbursement. Similarly to their US counterparts, informants representing outcomes

research and PAR stressed the need for on-going education about the importance of RE, "…the biggest barrier is to change the thinking and the perspective of the (clinical) development force. Most of them are not trained on these concepts of relative effectiveness – what it essentially means and why it is important. Many of them do not even consider that important. So they are not trained to understand or to incorporate it into developmental strategy. The biggest challenge and the biggest barrier is to first inform them with all of this information and then enable them to change their trial design, patient population, the competitors or the evidence generation strategy according to the needs of the market or to the patient or to the HTAs because they are focused only on the regulatory approval." This group also mentioned the importance of having an internal champion to help catalyse the change toward incorporating RE evidence considerations into development plans, as well as to help provide adequate resources to fund studies and attract and retain top talent to lead the RE research effort. One CER informant told us that to improve the pool of talent available, they are partnering with academic institutions to create drug development research fellowships to expand training opportunities.

4.3.2 External barriers and facilitators to CER/RE

Both the clinical development and outcomes research informants highlighted the difficulties of trying to be responsive to the complexity of payer requirements globally when they often differ in terms of appropriate comparators and other evidence requirements. One outcomes research informant stated, "I think that the actual barriers that are issues for us are different people wanting different data, the types of data, and how do you prioritise and understand who needs what. And can you deliver it. I think the evolution of, for example, the HTA groups and the way that countries assess value and the need for comparative effectiveness data is a sort of a moving target." A few of the clinical development key informants also mentioned that producing evidence for HTA bodies is "essentially redoing what the regulator is doing because a large part of the HTA is benefit/risk." This uncertainty in evidence requirements and perceived duplication of oversight in the EU without clear standards was widely perceived to be a barrier to more seamless integration of CER/RE into drug development programs. Additional barriers that were mentioned by US interviewees were the lack of electronic health records in certain countries and lack of knowledge of disease epidemiology in certain geographies such as China. Also cited were limited opportunities to partner with delivery organisations to utilise "big data" to facilitate the conduct of CER based on clinical care data (these organisations are sceptical of motivations of the pharmaceutical industry and would prefer to conduct studies independently). Finally, others cited how medical schools and schools of public health have not kept pace with the changing environment and not produced clinicians and researchers that are trained to appreciate or conduct CER.

External facilitators of CER/RE would be greater harmonisation of the evidence requirements so there would be less complexity in the corresponding study designs. In the US, the biggest facilitator would be if FDA started to require CER as part of the approval process. Also, financial pressures from the health care reform agenda will act as a facilitator for CER. These external challenges, as argued by few informants, will help influence internal decision making processes in companies. Finally, several of the key

informants that were interviewed from the RE perspective stated that was what needed to facilitate the integration of RE was case examples of assets that had recently gone through this process and had been thoroughly analysed for what worked and what did not work in order to improve the process for future compounds.

4.4 Future direction of the CDDP

4.4.1 Perspectives regarding the relative importance of CER/RE by the year 2020 and why

The key informants all felt that the importance of CER/RE would only grow by the year 2020 – this was due primarily to the predicted continued demand from payers for evidence of the new drugs as demonstrated through comparative studies. Other factors responsible for the increasing expectations for CER/RE over time include the explosion in available interventions to treat and prevent disease and the desire to make evidence-based decisions on the part of clinicians, patients and payers. Several interviewees mentioned that current investment in critical enablers such as electronic health records, research partnerships between delivery systems and industry, training of new researchers and methods development would likely facilitate the uptake of CER/RE within the industry. One interviewee pointed out that the results of studies launched in 2013-15 will be available by 2020 and the insights from these initial studies will "transform the way we think about how we launch medicines and collect data on them."

4.4.2 What do you predict will be the biggest process changes compared to how drugs are developed and commercialised today?

The interviewees in general believed that by 2020 the drug development process would have changed because by that time CER/RE evidence requirements would be more predictable, transparent and harmonised. There would also be greater standardisation of CER/RE methodologies, as well as of the interpretation and reporting of study findings. The result at the level of project teams would be that drug development plans reflect CER/RE evidence considerations early and consistently on teams, reflecting widespread understanding of the importance of this information for reimbursement and patient decision-making in addition to achieving the traditional regulatory approval for the compound. Many interviewees stated that they hoped that since much of the CER/RE data (or at least elements of it, such as relative efficacy data i.e. having a head to head comparative study) are now being collected in phases III and IIIb, drugs could receive conditional approvals earlier with a requirement for observational studies post-approval or those regulatory agencies would accept observational studies for approval. The net effect would be to try to balance the increased evidence requirements of CER/RE with innovative regulatory strategies so that drug development timelines would not inevitably be extended. However, there still needs to be a demonstrated return on investment for the industry in terms of reimbursement and market access to justify the incremental investments in CER/RE.

4.4.3 What factors (internal or external) are likely to be the biggest drivers of these changes?

In Europe, the biggest drivers mentioned consistently by the informants were the pressure from payers to contain costs and the corresponding demand for evidence of the cost-effectiveness of new medicines. This was characterised as a practical approach to a real-world problem, but the expectation on the part of the interviewees was that there was going to be greater transparency from the payers regarding acceptable methods and comparators and ideally more effective communication between regulators and payers. In parallel, several key informants mentioned that the results of current HTA studies should be a driver of future studies as the industry builds a credible evidence base for RE discussion going forward.

In the US, key informants described the evolution in health information technology as a major driver of the changes in CER, specifically enabling real-world clinical trials with cluster randomisation where patients can be followed "for the rest of their lives." Others also described the important role of patients and patient advocacy groups in both research priority-setting at the political level as well as influencing specific study designs. Interestingly, only one interviewee spontaneously mentioned PCORI, although when prompted, several others stated that they were planning on tracking future developments of this organisation, specifically methods development.

4.4.4 Additional comments

One interviewee from clinical development in the US said that all companies need to do longer-term outcomes studies to show the impact of their therapies – but he pondered whether this was indeed CER. If direct comparisons are not involved, the distinction may not be clear – "you are kind of breaking new ground in a way."

In Europe, and as mentioned already, one of the biggest issues is the choice of active comparators as this has huge cost implications for the clinical development program. Greater acceptability of indirect comparison data would have a huge impact on industry as there would not be the need to prospectively study all the relevant active comparators for the major markets.

The pharmaceutical industry has typically relied on clinicians to provide insights regarding what matters to patients. Many of our interviewees stated that they recognised that their companies needed to do a better job of engaging patients directly.

5 SUMMARY

The purpose of this work has been to ascertain how the CDDP at five global pharmaceutical companies is evolving in response to perceived demands for evidence of comparative effectiveness and relative effectiveness, in particular, from payers and HTA bodies, but also from clinicians and patients. To accomplish this goal, we first undertook a targeted literature review, followed by a semi-structured interview program with an international sample of 19 senior executives (12 identified as CER experts and seven as RE experts).

Both tasks have revealed a number of common emerging themes regarding both CER and RE, and more importantly, how companies are adapting to this new environment which is elevating the importance of information needs of these post-regulatory decision-makers.

First, the current drug development paradigm has already started to change in response to CER/RE evidence demands from stakeholders. Companies are increasingly asking how most new drugs compare with existing or potential alternatives in terms of unmet medical needs, comparative advantages and plausible value proposition. While amongst our interviewees, only a few are considering CER/RE before phase I, the majority do so by phase II, and nearly all have incorporated CER/RE evidence requirements to some degree by phase III. These changes range from inclusion of active comparators in clinical trials, inclusion of stakeholders to help define key phase IIb and III study design features, inclusion of PRO measures and earlier planning for phase IV studies. It is also true, however, that some of these changes do not deliver on all the elements of CER/RE, particularly the "under usual circumstances of care" dimension. However, our key informant interviews highlighted the need for industry to improve on current methods for eliciting the patient perspective, as their current conceptualisation of CER/RE tends to be primarily payer-focused.

It should be pointed out that our literature review and questionnaire focused on CER/RE, excluding other terms that are often used as synonyms e.g. HEOR. We believe that it is likely true that all companies consider unmet medical need and potential product differentiation before phase I, but so little is known at that point about the potential product profile that it is probable that most respondents would not call these discussions CER/RE, although a few may. Thus, the above statements from the interviews should be taken with the caveat about whether some of the apparent differences we find reflect real differences between companies, as opposed to different usage of terminology.

These findings are consistent with the characterisation of CER/RE in the literature, which highlighted the need for companies to ensure that drug development needs to adapt to requirements driven by payers and HTA bodies and not to solely focus on regulatory requirements. This should involve liaising with payers and HTA bodies, at least in phase II trials to ensure that new products can generate and translate additional value propositions for multiple audiences. Some commentators even argue that if manufacturers want to remain competitive in the changing environment and improve their financial success, they must incorporate payer requirements into each stage of their development process and understand what evidence is more relevant in

reimbursement decisions (Schoonveld, 2011; Epstein, 2012; Lalonde and Willke, 2011). Moreover, a recently report published by Avalere supports the findings from our interview programme that over the past decade, the pharmaceutical industry has "sought to recalibrate development and commercialisation approaches and processes for new products. These efforts have included greater and earlier engagement with public and private payers; investments in CER to better produce credible, relevant and timely research; and reinforcing its role as a trustworthy and full partner to patients, clinicians, payers and government in the pursuit of quality improvement and value" (Avalere, 2013).

In 2013, Woodcock, the Director of the FDA Center for Drug Evaluation and Research (CEDR) discusses in an editorial the challenges in CER, focusing in the US. She argues that the drive for CER is the need for more reliable information to guide clinical decision-making. In her opinion, regulators aim for a very low probability of making a wrong decision. She also claims that "new methods for obtaining reliable information must be brought to bear. These methods may not need to be as robust as those used for regulatory purposes; however, they must yield results that are significantly more reliable than the anecdote, intuition and traditional approaches that have served us poorly in the past. A trade-off between reliability and feasibility is the likely evolving point of friction between the CER and product development enterprises" (Woodcock, 2013).

Second, CER/RE investments are being made at different phases depending on the company. Not surprisingly, however, CER/RE investments currently lag behind the phases of initial evaluations which typically involve project team discussions with representatives from HEOR and PAR and the development of initial product profiles and models of expected product effects on clinical outcomes relative to alternative treatments. If the investigational compound progresses beyond these initial evaluations (including the requisite safety and early efficacy requirements), then typically the project team leader would advocate for the incremental investments to be made in the clinical development program to support CER/RE data collection. Again, the majority of our informants stated that their companies usually start these investments in phase IIb and IIIa, but some start as late as phase IV. However, most companies are currently building active comparators into at least some of their phase III programs. It is worth noting that some of these changes relate more to relative efficacy rather than CER/RE, as they do not the address the "under usual circumstances of care". The degree to which they focus on this currently in the US as compared to Europe is less, given that the EU has a longer experience of responding to the demands of national HTA/pricing and reimbursement bodies.

Third, a number of barriers have been identified in terms of incorporating CER/RE considerations into companies' drug development plans. While we spoke to a group of individuals that could be characterised as "early adopters" of CER/RE, they identified a number of existing internal barriers to the successful integration of CER/RE within companies. These included a lack of clear accountability for incorporating CER/RE considerations into development plans, and lack of incentives, given companies' focus has been historically on regulatory approval. While many understand the need for incorporating the payer perspective into drug development decisions, it is often difficult

to change pharmaceutical companies' decision-making processes, yet this will be a necessary step for the inclusion of CER/RE within drug development (Schoonveld, 2011). Organisational adaptations will be essential such as aligning development teams more closely with HEOR teams and with the commercial side of the organisation (vanNooten et al., 2012).

The costs of undertaking such studies were also mentioned as a barrier. This raises a key trade-off for companies: implementing CER within drug development in the US and incorporating RE requirements into clinical development will lead to bigger and more expensive trials (Eichler et al., 2011). Thus, companies will need to ascertain the return of investment (ROI) of undertaking such new initiatives. However, we are not aware of any evidence estimating the magnitude of these additional costs or the returns from them

Another barrier raised was the lack of shared understanding on the development team of the importance of external demands for CER/RE data, together with the lack of confidence amongst scientific staff that today's experts have sufficient methods or adequate data to generate robust/valid data from CER/RE studies. This situation is exacerbated by a lack of trained CER/RE researchers, although a few key informants mentioned that industry was playing a leadership role in helping to train future researchers.

Fourth, a number of facilitators to the successful integration of CER/RE were identified, one being an internal champion, often a very senior member of the company, who could provide leadership and support. A second facilitator identified was the ability to attract and retain top talent to lead the CER/RE research effort. And third, external pressures and drivers for CER/RE to support market access and reimbursement ultimately help overcome internal resistance within companies.

Fifth, there was universal agreement on the part of our interviewees that by the year 2020, CER/RE would have a much greater role in influencing the process of drug development as compared to today. The biggest drivers for this increased role include: payer demands for evidence of product value because of continuing pressures to contain rising healthcare costs; increases in the number of therapeutic alternatives within the therapeutic class and the desire on the part of payers, patients and clinicians to make evidence-based decisions to choose amongst these alternatives; advances in electronic health records, clinical research infrastructure and observational data methods that would all serve to enable the use of real-world data and practice-based research; and patient and consumer demand for better evidence to support their decision-making (primarily in US). However, several interviewees did signal the cautionary note despite the recognition on the part of the industry that CER/RE had become part of the marketplace's evidence expectations.

To achieve specific aims that are essential to the successful conduct of CER/RE, regulatory paradigms may need to be adapted. These aims include a full exploitation of biomarker strategies for optimisation of the treatment-eligible population, mechanisms for balancing the need for early access by patients with a high degree of unmet need with the ethical imperative to not exclude other patients from potentially beneficial

treatments, and continued means for keeping the drug development process efficient and sustainable (Eichler et al., 2011).

Regulators do continue to attempt to address this issue, in some cases with forward-looking initiatives. For example, the EMA in 2011 launched its Road Map to 2015, which describes three priority areas for the Agency's work, one of them under the heading "facilitating access to medicines" including "facilitating new approaches to medicine development" (EMA, 2011b). EMA also intends to "continue to review the model for regulation of medicines in the EU, particularly with regard to the development of medicines, the benefit/risk balance and the growing importance of HTA bodies" (EMA, 2011b). In conclusion, the observed CDDP, as described by senior executives at five large global pharmaceutical companies, mirrors in many ways the trends described in the literature regarding rational responses to marketplace demands for CER/RE evidence to support decision-making about new drugs.

6 CONCLUSIONS

CER and RE have at least two distinct key concepts embedded in their definitions: *relative/comparative* and *real life/usual practice conditions*, as revealed by our interviewees. However, the relative importance of these two concepts in driving the design of CER and RE studies is currently not clearly defined within individual companies. Some company representatives classified a Phase III registration study with an active comparator as an example of a CER study, while others stated that it was impossible to do a "real" CER study prior to Phase IIIb or even IV. To further explore their importance we need to assess what seems to be the focus of regulators (FDA/EMA) and national payers/HTA bodies.

From the FDA and EMA perspectives, CER and RE broadly defined are not universally required for regulatory approval. However, relative efficacy can be, especially in Europe – but primarily related to active comparator studies (rather than the 'real life' dimension). Although as mentioned above, EMA is increasingly interested in monitoring the benefit of a medicine as well as its risks, throughout its life cycle - it has become increasingly important to ensure that drugs continue to be safe and effective post-launch. Also, the FDA is increasingly focusing on the need for comparative effectiveness data. As argued by Woodcock, Director of the Center for Drug Evaluation at the FDA, "new methods for obtaining reliable information must be brought to bear. These methods may not need to be as robust as those used for regulatory purposes; however, they must yield results that are significantly more reliable than the anecdote, intuition and traditional approaches that have served us poorly in the past. A trade-off between reliability and feasibility is the likely evolving point of friction between the CER and product development enterprises" (Woodcock, 2013). It appears that Dr. Woodcock is primarily viewing CER as providing complementary data to those obtained from traditional registrations trials. A follow-up question, which is unresolved currently, is whether regulatory agencies, such as FDA and EMA, would accept observational studies for approval. There are also challenges of doing real world studies pre-launch, where the ability to liberalise entry criteria and simplify data collection may be limited given the investigational drug status, regulatory requirements and potential safety concerns.

From the payers and HTA bodies' perspective, the preponderance of evidence suggests that they are pursuing both concepts (CER and RE) in their desire to achieve 'value for money' from new medicines. These stakeholders want to reimburse new medicines that offer added value, especially if at a price premium, relative to existing alternatives. In order to achieve that, they are seeking comparative evidence in their real life settings. For example, both the German and French reimbursement systems require comparative trials and will not consider other methodologies (Gerber et al., 2011; Mauskopf et al., 2011; Benkimoun, 2011) – however, as clinical trials are not usually done in real life settings, these systems are looking more for relative efficacy than effectiveness, at least at launch. NICE, in its latest Methods Guide (NICE, 2013), does not define RE, but defines "clinical effectiveness" as "the extent to which an intervention produces an overall health benefit, taking into account beneficial and adverse effects, in routine clinical practice. It is not the same as efficacy" (NICE, 2013, page 85). This is very similar to the RE definition used for this work. While CER and RE do not include the

explicit analysis of costs and prices, by assessing effectiveness, these studies do provide a key input to measure the cost-effectiveness of new medicines. Moreover, there are differences across payers/HTA bodies in the US and Europe in terms of a systematic use of cost effectiveness in their decision making process, and some countries just focus on clinical effectiveness (which is thus more akin to our CER/RE concept). Given that companies have acknowledged the important gate-keeper role of payers, most clinical development teams are currently building active comparators into at least some of their phase III programs. The degree to which they focus on this currently (2010-2012) in the US as compared to Europe is less, given that the EU has a longer experience of responding to the demands of national HTA/P&R bodies.

Increasingly, relative efficacy information and other evidence needs for payers is viewed as mandatory in many European markets– but again, to what extent can this additional evidence be viewed as meeting the traditional definition of RE? Are these evidentiary needs about real world studies or just putting a comparator arm in a clinical trial primarily designed for registration? The results from our interviews reflect differing viewpoints on this, as some of the changes just described only reflect one dimension of CER/RE – the 'relative' aspect. In the US, there was much more discussion about alternative data sources and study designs that would address the pragmatic features of CER, such as the use of registries, large simple trials, observational studies and electronic health records. Nevertheless, there still remained an absence of clarity within and across companies regarding the essential features of a CER study and whether these types of studies could actually start as early as Phase II. In addition, we were asked to consider other internal and external forces not directly related to these new requirements. For instance, companies are trying to reduce R&D costs and third party payers are trying to control health care costs, especially during the last few years where public financial resources have been limited. These downward pressures on drug development costs would typically incentivise companies to look for ways to reduce trial costs, thereby avoiding the simplistic approach of routinely investing in multi-arm, active comparator phase III trials to satisfy multiple payer decision-makers.

To achieve specific aims that are essential to the successful conduct of CER/RE in the future, a number of issues need to be resolved. First, whether industry, HTA bodies and regulators can be expected to work more closely together in designing drug development plans, to generate the information required for both approval and post-approval decision-making. This could be achieved building from existing initiatives, such as the Mini-Sentinel project in the US. Related to this point is the feasibility of drugs receiving conditional approvals earlier with a requirement for observational studies post-approval or those regulatory agencies accepting observational studies for approval. In addition, there is the possibility of greater use of pragmatic trials, where patients are randomised to various treatments and then simply followed with very few protocol-mandated interventions, trying to emulate real-world practice conditions as much as possible. These trials may be conducted either pre-or post-approval, depending on the particular drug and clinical context but they remain an important study design option as the pursuit of novel methods and more cost-effective data collection converge in the service of developing more informative evidence for a broader array of decision-makers.

Second, what is the feasibility of confirmatory phase III study designs with more two or three-arm active controlled trials to demonstrate superiority or non-inferiority? This has important implications for industry. Non-inferiority is a higher and more risky bar for companies, which is why they may still prefer to have regulators use placebo, even if this means doing additional evidence collection for payers. As mentioned above, it is possible, especially in Europe, for companies to use comparator studies for registration. This would avoid the apparent inconsistencies of having placebo trials for registration and comparator trials for payers. But companies might want to face this inconsistency, rather than have registration require comparator trials.

On a related point, will there be greater acceptability of indirect comparisons? And if so, will greater use of indirect comparisons discourage head to head trials with an active comparator (relying on placebo control as the common link) or encourage the use of one good large head-to-head with other comparisons made indirectly? Indirect comparisons carry a risk of their own, as they tend to be less reliable that head to head or direct comparisons, plus some HTA agencies, such as in Germany, currently give little weight to indirect comparisons.

Third, what would be the impact of CER/RE evidence requirements on the costs of drug development? These requirements are expected to increase costs, presumably due to a number of different factors. These include larger sample sizes to prove added value relative to active comparators and/or adding multiple comparators to satisfy different payers in multiple countries. Pharmaceutical companies may need to realign their development processes to maximise their resources and make efficient choices towards managing these trade-offs. One approach that companies are taking is to use CER/RE considerations in determining which drugs are chosen to progress in drug development, such that drugs with a "poor" CER/RE profile are stopped or redirected.

Fourth, how can internal processes in drug companies enable closer collaborations between clinical development, medical affairs, HEOR and pricing and market access staff? While these groups have been encouraged to collaborate for decades, the marketplace demands for CER and RE evidence are at a critical point of confluence and are universally perceived to only grow in magnitude and importance over the next five to seven years by our interviewees. Therefore now is the time for companies to invest in training and ensuring that there are the appropriate incentives and rewards for project teams that develop drugs with robust comparative evidence that includes the perspectives of patients and other stakeholders.

Again, while these are difficult questions to answer, the reader is encouraged to consult two related lines of investigation that are associated with this study. The first is an investigation of the changing evidence requirements of payers as they were asked to evaluate various types of CER and RE data for hypothetical cases to support coverage and reimbursement decision-making (Moloney et al., sumbitted). The second is a Delphi study, which explored key factors influencing future evidence expectations for the production of evidence from CER for drugs by the year 2020. (Messner et al., sumbitted). Taken together, these three reports provide a more complete overview of the changing CER/RE environment for the pharmaceutical industry currently, as well as projected over the next five to seven years. What emerges is a clear demand and

direction for revising the CDDP, while continuing to look for additional ways to overcome organisational barriers to change, improve drug development efficiencies and include stakeholder perspectives.

APPENDIX 1 METHODOLOGY AND BIBLIOGRAPHY OF ARTICLES INCLUDED IN THE LITERATURE REVIEW

We conducted a literature review to

1. Assess how CER and RE evidence requirements have been described as likely to impact the CDDP; and

2. Inform and guide the development of the semi-structured interview guide for the qualitative interviews with industry experts.

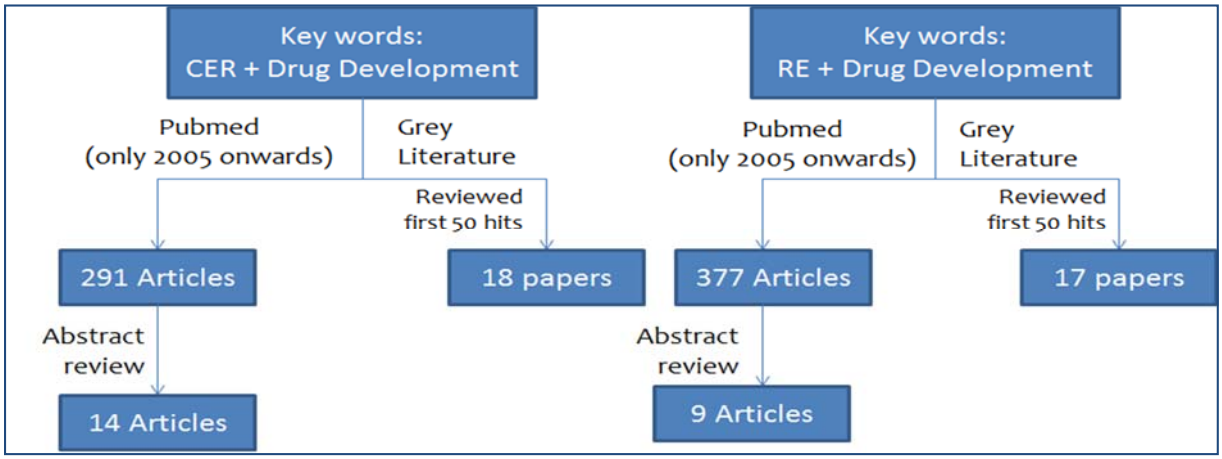
To identify published literature relevant to this review, we used the search terms "Comparative Effectiveness Research + Drug Development" and "Relative Effectiveness + Drug Development". We searched PubMed, Google, and Google Scholar to adequately capture the most relevant literature in the peer reviewed and grey literature, as we knew that some of the relevant information would not have been published in the peer-review literature (which was indeed the case). Inclusion criteria for selecting literature to be included in the literature review were as follows: published 2005 or later, published in English, full publication (excluded articles only available as abstracts), and contributed significantly to the understanding of the role played by CER/RE in the current drug development paradigm.

Data abstraction was performed by the authors who reviewed the CER literature (Emily Rosenberg (ER)) and RE (Michele Pistollato (MP)) literature respectively. Both groups followed the same approach to identify the relevant hits: two researchers in parallel reviewed the title and abstracts of all the papers identified (ER and Patricia Deverka for CER and MP and Jorge Mestre-Ferrandiz for RE). Papers selected by only one of the two researchers were discussed and agreed by both whether they would be selected or not. The most relevant data were abstracted from each article, following an agreed structure, summarised, and inserted into Excel spreadsheets, each with eight fields that captured the overarching themes of the project. The data captured in these spreadsheets was then used to inform this paper along with the key informant interview data.

A total of 32 papers met the selection criteria for 'CER and drug development' while 26 papers were similarly chosen for 'RE and drug development' (Figure A2.1). Three papers were overlapping between the articles identified and used from the two different keyword searches therefore the literature review finally considered a total of 55 papers (32 + 26 – 3).[5]

[5] The three overlapping papers are: Doyle JJ. The effect of comparative effectiveness research on drug development innovation: A 360° value appraisal. J Comp Effec Res 2011;2011(1):27-34.); Honig PK. Comparative effectiveness: The fourth hurdle in drug development and a role for clinical pharmacology. J Clin Pharm Ther 2011;89(2):151-156; Lalonde RL, Willke RJ. Comparative efficacy and effectiveness: An opportunity for clinical pharmacology. J Clin Pharm Ther 2011;90(6):761-763.

Figure A2.1. Publication selection process overview



As stated in the main text, the main purpose of this literature review was to ascertain the impact of RE/CER on drug development. Those abstracts that did not consider this issue were not included in the final review.

For the purpose of organising the literature review and summary, the research team developed an article abstraction structure:

- Current demand for CER/RE;
- New types of CER/RE evidence required;
- Recommended methods for conducting CER/RE;
- Current Impact of CER/RE on Drug Development;
- Expected (future) impact of CER/RE on Drug Development;
- Future use of evidence for end user;
- Facilitators to widespread use of CER/RE; and
- Barriers to widespread use of CER/RE.

APPENDIX 2 INTERVIEW GUIDE

Describing your company's current approach to drug development

Key Informant Interview Discussion Guide

External Version for Comparative Effectiveness Research Informants

Introduction

You have been selected to speak with us because of your in-depth knowledge of your organisation's current (2010-2012 timeframe) drug development process and how your organisational role is related to that process. This interview will be kept confidential. The results from all of the interviews will be collected, combined with information from the other four companies participating in the project, and only reported in the aggregate. There will be no individual or company-specific identifying data in the final report. Please note that though we may use direct quotes in the final paper, we will not attribute any quote to a specific person or organisation.

To facilitate our note-taking, we would like to audio tape our conversation today. For your information, only researchers on the project will listen to these tapes to ensure that we have accurately summarised your responses, and the tapes will be destroyed upon completion of the project.

We have planned the interview to last no longer than one hour. During this time, we have a range of questions we would like to cover. We will do our best to direct the conversation so that we cover all of the questions in the time allotted.

Objectives and Goals

The overall objective of the New Drug Development Paradigm project is to develop alternative scenarios of how the demand for comparative effectiveness research (CER) in the US and relative efficacy/effectiveness (RE) in EU is likely to influence the industry's approach to drug development by the year 2020. To facilitate this goal, we are interviewing key experts in drug development and commercialisation who can inform us about the Current Drug Development Paradigm (CDDP) and the ways in which it may already be responding to meet the evolving requirements of payers, Health Technology Assessment bodies, and regulatory agencies for increased evidence of comparative/relative effectiveness and value. We anticipate that the interview questions will vary slightly depending on whether the respondent is primarily involved with the commercial or clinical development side of the organisation. We have also tailored the interviews so that each respondent is asked specifically about either CER or RE. This interview will focus on CER. Once all of the interviews are completed, we will analyse and compile the data and combine it with the literature review in a white paper that will be submitted for publication. The paper will be shared with you in early 2013 via your company effort leader.

This interview has four main goals. First, we seek to assess your views on CER, including how you define this concept. Second, we will ask questions regarding your company's CDDP to understand the ways in which it has been adapted or is currently adapting to stakeholder evidence requirements and information needs in the CER space. Next, we

will ask for your perspective regarding possible factors that may facilitate or hinder the process of adapting the CDDP to external demands for additional CER evidence. Finally, we will ask you to provide your opinion of the future direction of the CDDP in this context, in particular how you see the CDDP evolving over the next 5-7 years.

Preliminary Background Information About You

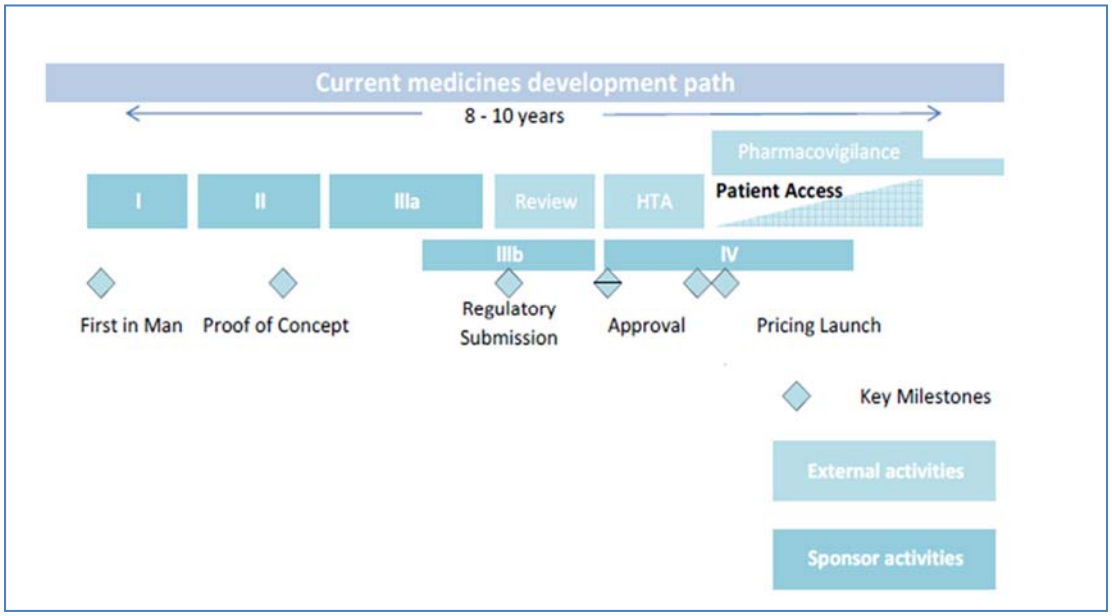
(Please note: We will try to complete these questions prior to the interview as much as possible and simply confirm the information during the interview).

1) Where are you located? What geography(s) do you cover?
2) What is your current position and job title? How many years have you worked in your current position?
3) What is your professional background?
4) How many years have you worked in the pharmaceutical industry as a whole?

Part One: CER Definitions and Differentiating Features

1) What is your working definition of Comparative Effectiveness Research (CER)?
2) What do you consider to be the most unique features of CER as relates to designing studies? As relates to regulatory approval? As relates to market access and reimbursement?
3) Do you see CER as a disruptive change for the pharmaceutical industry (a substantial new evidence requirement) or a more modest expansion or continuation of existing evidence demands?

Part Two: Current Drug Development Paradigm (CDDP)



Source: Barker, 2011.

4) Does this traditional figure accurately characterise your CDDP? If not, how does it differ?

5) Have you recently (2010-2012 timeframe) started to change the CDDP to address CER information needs?

Probe: If yes, proceed with the following questions (starting with Q6). If no:

   a. Please describe whether you feel your current health economics and outcomes research (HEOR) evidence development process is relevant to the CER discussion. Please note that your organisation may call this process by a different name, such as "pricing, reimbursement and market access."

6) At what stage of drug development in the CDDP is CER first considered?

7) At what phase(s) are CER investments being made?

8) Has CER affected portfolio management decisions, e.g., Go/No Go decisions?

9) How do CER considerations vary by product type? For example:

   a. New drug of relatively high cost that is effective in a small population of patients;

   b. New drug that demonstrates marginal difference in effect on hard endpoints in phase III trials, compared to its competitors (this drug uses a more convenient route of administration than existing competitors that do not require visits to the doctor's office;

   c. Drug for a disease where no alternative treatment exists.

10) Are external stakeholder groups such as payers, patients, and clinicians consulted? If so, how?

11) Are CER-related protocols developed globally or are they typically country-specific? In particular, what are the differences/similarities in such protocols between the US and Europe?

12) Do you see opportunities to harmonise CER evidence requirements across countries?

13) In what ways do you see opportunities for CER to contribute information to the benefit-risk assessment?

14) Do you see any conflicts or synergies between the goals of CER and the goals of developing drugs and companion diagnostics?

Part Three: Factors affecting whether and how CER is influencing the CDDP

15) What group(s) at your organisation are responsible for ensuring that CER considerations are incorporated into the CDDP?

   a. Who are the internal decision-makers?

b. Who are the internal stakeholder groups?

16) Given that some changes are currently underway to adapt your company's CDDP to the CER needs of payers, clinicians and patients, what are the biggest internal barriers to change? (Top 3)

17) What are the biggest external barriers? (Top 3)

18) Are there other external facilitators of change? (Top 3)

Part Four: Future Directions

19) Imagine that it is now the year 2020. Do you feel that compared to today CER will be a more or less important factor influencing drug development and market access/reimbursement planning in the geographic area that you cover?

a) Why do you feel that way?

20) What do you predict will be the biggest process changes compared to how drugs are developed and commercialised today? *(Probe: Ask for their top 3 changes)*.

21) What factors (either internal or external) are likely to be the biggest drivers of these changes?

22) Is there anything else that we haven't yet covered that you would like to share, that you think is relevant for our project team's understanding of how CER is influencing the CDDP at your company?

APPENDIX 3 GLOSSARY

Term	Definition
Benefit-risk assessment	The process of assessing the benefits and risks in the context of a new drug application. *Source: Committee For Medicinal Products For Human Use (CHMP), Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use, London, 2008.*
Clinical Practice Guidelines	Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (Institute of Medicine, 1990). They define the role of specific diagnostic and treatment modalities in the diagnosis and management of patients. The statements contain recommendations that are based on evidence from a rigorous systematic review and synthesis of the published medical literature. *Source: National Heart, Lung and Blood Institute.* http://www.nhlbi.nih.gov/guidelines/about.htm
Clinical Trial	In a clinical trial (also called an interventional study), participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behaviour, for example, diet. Clinical trials may compare a new medical approach to a standard one that is already available or to a placebo that contains no active ingredients or to no intervention (http://clinicaltrials.gov/ct2/info/understand).
Comparative Effectiveness Research	CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.
European Medicines Agency	The EMA is a decentralised agency of the European Union, located in London. It is responsible for the scientific evaluation of medicines developed by biopharmaceutical companies for use in the European Union.
External Validity	The degree to which results of a study may apply, be relevant, or be generalised to populations or groups that did not participate in the study. *Source: Porta M, A Dictionary of Epidemiology, Oxford University Press, 2008.*
Food and Drug Administration	The FDA, part of the US Department of Health and Human Services, is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, and veterinary products.

Term	Definition
Health Economics and Outcomes Research (HEOR)	HEOR is defined as a scientific discipline that quantifies the economic and clinical outcomes of medical technology. It helps manufacturers of pharmaceuticals and devices communicate the value of their innovations to stakeholders. It is becoming a central component for demonstrating product value which encompasses aspects such as clinical efficacy, real-world data, patient quality of life reports, opportunity cost of various treatment mixes, budget impact, and cost-effectiveness models, which eventually supports the allocation of resources for the acceptance and reimbursement of new products (http://basecase.com/articles/heor-value-in-healthcare/).
Health Outcomes	The term refers to the impact healthcare activities have on people — on their symptoms, ability to do what they want to do, and ultimately on whether they live or die. Health outcomes include whether a given disease process gets better or worse, what the costs of care are, and how satisfied patients are with the care they receive. It focuses not on *what is done* for patients but *what results* from what is done (http://myhealthoutcomes.com/faqs/3000).
Health Technology Assessment (HTA)	Health technology assessment (HTA) is a form of policy research that examines short- and long-term consequences of the application of a health care technology. The goal of HTA is to provide policymakers with information on policy alternatives. For any given technology, properties and impacts assessed may include technical properties (this is particularly germane for sophisticated equipment), evidence of safety, efficacy (including patient-reported outcomes), real-world effectiveness, cost, and cost-effectiveness as well as estimated social, legal, ethical, and political impacts. Thus, HTA is conceived as being much broader than is typically true of health and economic outcomes research of a health care technology (http://www.ispor.org/terminology/default.asp).
Indirect comparisons	The use of meta-analytic techniques to compare arms of different randomised controlled trials. Since the benefit of randomisation does not hold across trials, indirect comparisons are more prone to bias than direct head to head comparisons. *Source: Glenny AM et. al. (2005) Indirect comparisons of competing interventions. Health Technology Assessment. Vol. 9: No. 26. Available here: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0007/64951/FullReport-hta9260.pdf.*
Internal Validity	The degree to which a study is free from bias or systematic error. *Source: Porta M, A Dictionary of Epidemiology, Oxford University Press, 2008.*
Meta-analysis	A statistical analysis of results from separate studies, examining sources of differences in results among studies, and leading to a quantitative summary of the results if the results are judged sufficiently similar to support such synthesis. A frequent application is the pooling of results from a set of randomised controlled trials, which in aggregate have more statistical power to detect differences at conventional levels of statistical significance. Meta-analysis has a qualitative component (i.e. classification of studies according to predetermined characteristics

Term	Definition
	such as study design, completeness and quality of data) and a quantitative component (i.e. extraction and analyses of the numerical information). The aim is to integrate the findings, if possible, and to identify overall trends or patterns in the results. Studies must be subject to critical appraisal, and various biases in the selection of subjects, decision of events or presentation of results must be assessed. *Source: Porta M, A Dictionary of Epidemiology, Oxford University Press, 2008.*
Non-inferiority	Non-inferiority trials are intended to show that the effect of a new treatment is not worse than that of an active control by more than a specified margin. *Source: Snappin SM (2000) Curr Control Trials Cardiovasc Med.;1*(1)*: 19–21.*
Observational Studies	A study in which participants are not randomised or otherwise preassigned to an exposure. The choice of treatment is up to patients and their physicians (subject to third-party payer constraints). *Source: Berger M et al. (2012) Prospective observational studies to assess comparative effectiveness: ISPOR Good Research Practice Task Force report. Value in Health 217-230.*
Patient Reported Outcomes Measures (PROMs)	A patient-reported outcome measure (PROM) is a series of questions that patients are asked in order to gauge their views on their own health. PROMs are completed by patients themselves. The purpose of PROMs is to get patients' own assessment of their health and health-related quality of life. (Appleby and Devlin, (2010) *Getting the most out of PROMs: Putting health outcomes at the heart of NHS decision making.* London: Office of Health Economics). Measures include such outcomes as global impressions, functional status, well-being, symptoms, health-related quality of life (HRQoL), satisfaction with treatment, and treatment adherence (http://www.ispor.org/terminology/default.asp).
Patient-Centered Outcomes Research	Patient-Centered Outcomes Research (PCOR) helps people and their caregivers communicate and make informed health care decisions, allowing their voices to be heard in assessing the value of health care options. This research answers patient-centered questions such as: 1. "Given my personal characteristics, conditions and preferences, what should I expect will happen to me?" 2. "What are my options and what are the potential benefits and harms of those options?" 3. "What can I do to improve the outcomes that are most important to me?" 4. "How can clinicians and the care delivery systems they work in help me make the best decisions about my health and healthcare?" To answer these questions, PCOR: • Assesses the benefits and harms of preventive, diagnostic, therapeutic, palliative, or health delivery system interventions to inform decision making, highlighting comparisons and outcomes that matter to people; • Is inclusive of an individual's preferences, autonomy and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health related quality of life; • Incorporates a wide variety of settings and diversity of participants to address

Term	Definition
	individual differences and barriers to implementation and dissemination; and • Investigates (or may investigate) optimising outcomes while addressing burden to individuals, availability of services, technology, and personnel, and other stakeholder perspectives. (http://www.pcori.org/research-we-support/pcor/).
Patient Reported Outcome (PRO)	Any reports coming directly from patients about how they function or feel in relation to a health condition and its therapy, without interpretation of the patient's responses by a clinician, or anyone else. ***Source:*** *Patrick D, Guyatt GH, Acquadro C. Chapter 17: Patient-reported outcomes. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008.* *Available from:* www.cochrane-handbook.org.
Payers	In health care markets, it is often the case that patients do not pay for the full cost of the technology they use – the difference between that patient pays and the full price is borne by a third party payer. In Europe, this third party payer can either be the public administration or the social insurance system. In the US there are many different categories of payers: (a) any insurance company authorised to provide health insurance in a state; (b) a health maintenance organisation; (c) a health care service contractor; (d) any legal entity that is self-insured and provides benefits for health care services to its employees; (e) any legal entity responsible for handling claims for health care services under a state or federal medical assistance program; (f) a Federal State or any local government within this state that makes payments for health care services; (g) any insurer authorised under the state law to transact workers' compensation or casualty insurance in this state; or (h) any employer authorised under the state law to self-insure its workers' compensation risk. (http://www.oregonlaws.org/glossary/definition/health_care_payor).
Phase I trial	Studies that are usually conducted with healthy volunteers and that emphasise safety. The goal is to find out what the drug's most frequent and serious adverse events are and, often, how the drug is metabolised and excreted. (http://clinicaltrials.gov/ct2/help/glossary/phase).
Phase II trial	Studies that gather preliminary data on effectiveness (whether the drug works in people who have a certain disease or condition). For example, participants receiving the drug may be compared with similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug. Safety continues to be evaluated, and short-term adverse events are studied. (http://clinicaltrials.gov/ct2/help/glossary/phase).
Phase III trial	Studies that gather more information about safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs. (http://clinicaltrials.gov/ct2/help/glossary/phase).

Term	Definition
	Sometimes Phase III trials are distinguished between Phase IIIa and Phase IIIb trials. Phase IIIa trials refer to trials conducted after efficacy of the medicine is demonstrated, but prior to regulatory submission. These clinical trials are conducted in patient populations for which the medicine is eventually intended. Phase IIIb trials refer to clinical trials conducted after regulatory submission, but prior to the medicine's approval and launch. These trials may supplement earlier trials, complete earlier trials, or may be directed toward new types of trials (e.g. quality of life, marketing) or Phase IV evaluations.
Phase IV	Studies occurring after a drug has been approved for marketing. These including post-market requirement and commitment studies that are required of or agreed to by the sponsor. These studies gather additional information about a drug's safety, efficacy or optimal use. (http://clinicaltrials.gov/ct2/help/glossary/phase).
Placebo	A placebo is an inactive drug, therapy or procedure that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness.
Pragmatic Clinical Trials	Clinical trials designed to assist health care decision-makers, referred to as pragmatic clinical trials (PCTs), are defined as trials for which the hypothesis and study design are formulated based on information needed to make a decision. *TunisSR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003; 290:1624-32.*
Pricing and Market Access	In some countries, after a drug receives the licensing approval decision, manufacturers need to negotiate the reimbursed price for its medicines with third-party payers (this is sometimes also called pricing and reimbursement and market access). This process will ultimately determine the uptake of new products. In some cases, this time period is negligible—days or weeks. However, in cases where a price and reimbursement determination must be made before marketing can commence, this period can be a few months to more than a year, and varies by country (European Federation of Pharmaceutical Industries and Associations (EFPIA), 2010, *Patients W.A.I.T. Indicator*. Brussels: European Federation of Pharmaceutical Industries and Associations).
Randomised Controlled Trial	An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body). *Source:* http://www.consort-statement.org/resources/glossary/q---z/randomized-controlled-trial/

Term	Definition
Registry [Methodology]	A record that chronicles information about all new disease cases, to gain an understanding of the demographic patterns and etiology of the disease. Ref: Clinical Trials Glossary. EURORDIS. June 2007. http://www.eurordis.org/IMG/pdf/CT_GLOSSARY_FINAL.pdf
Relative Effectiveness	Extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice. This is usually measured in observational and post-launch or pragmatic trial studies (High Level Pharmaceutical Forum, 2008)
Relative Efficacy	Extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions. This is measured in experimental settings using randomised controlled trials studies (High Level Pharmaceutical Forum, 2008)
Stakeholders	Individuals, organisations or communities that have a direct interest in the process and outcomes of a project, research or policy endeavour. *Deverka PA, Lavallee DM, Desai PJ, Esmail LC, Ramsey SD, Veenstra DL, Tunis SR. Stakeholder Participation in Comparative Effectiveness Research: Defining a Framework for Effective Engagement. J Comp Eff Res. 2012; 1(2):181-194.*
Superiority	When the aim of the study is to show that an experimental (E) treatment is superior to a control (C) treatment, the RCT is called a superiority trial and the associated statistical test is a superiority test. With a significant result, one concludes in a superiority trial that E is different in effect from C, and when the observed result is in favour of E, we conclude that E is statistically, significantly better performing than C. *Source: Bulletin of the NYU Hospital for Joint Diseases 2008; 66(2),150-4.*
Systematic Review	The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a special topic. Meta-analysis may be, but is not necessarily part of this. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardised methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary. *Source: Porta M, A Dictionary of Epidemiology, Oxford University Press, 2008.*

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