Identification of drivers of effectiveness in Hodgkin’s Lymphoma
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Key points
TBC

Background
Efficacy measured in clinical trials and effectiveness measured in real life studies are both important in decision making, any differences between the efficacy and effectiveness can introduce uncertainty into decision making. The reasons for a gap between efficacy and effectiveness (i.e., differences between clinical trials and real life studies that could impact the difference between efficacy and effectiveness estimates) can influence decisions as to whether a drug should be funded, and in which patients it should be prescribed. This literature review is part of the oncology case study of IMI GetReal Work Package 2 and is being undertaken to review the evidence relating to the efficacy-effectiveness gap in haematological malignancies.

Hodgkin Lymphoma (HL) was chosen as the initial area of investigation due to availability of patient level data for further analysis within the case study (out of the scope of this report), but this literature review was also expanded to the broader disease area of haematological malignancies in order to find any factor not explored in the HL setting but that could be informative in this setting.

Objectives
The key objectives of this literature review were to answer the following research questions:
1. Is there an efficacy-effectiveness gap in HL? What are the factors that could influence this gap?
2. What are the drivers of effectiveness in HL?

Methods
A systematic literature review was conducted consistently with the population, intervention, comparison, outcomes, study type and time horizon (PICOS-T) framework. The researchers searched in MEDLINE (using Embase.com Elsevier interface) and EMBASE (using Embase.com Elsevier interface) databases to identify the relevant literature. Search of key conference proceedings was limited to where the proceedings were available in a journal and therefore searchable via the database literature search. A general haematology search term was added to the HL disease-area search. This was to ensure that studies focusing on haematological malignancies that include Hodgkin lymphoma without indexing to HL or that papers encompassing efficacy/effectiveness aspects for several types of haematological malignancies relevant to HL were also captured. A time limit of 2000-2015 was set since before 2000 the concept of effectiveness was not well described. The search was restricted to articles published in English. First-pass screening of citations (titles and abstracts) and second pass screening (full text articles) were conducted independently by two
researchers. Any discrepancy between reviewers was reconciled by consensus. Hand crosschecking was performed to retrieve additional references. Data were extracted for the studies of interest from the full text of articles by two independent researchers, each performing the extraction independently. Any discrepancy between reviewers was reconciled by consensus. A total of 619 citations were identified through database search and underwent title/abstract review. Among those, 63 articles identified underwent full-text review. Hand crosschecking of references retrieved 5 additional references. A total of 42 articles were identified as eligible for data extraction. Among those publications, a total of 11 articles gave information based on HL patients.

Results

Hodgkin Lymphoma (HL)

Among the 11 studies reporting data on HL identified during this review, 5 gave information on efficacy/effectiveness gaps (Bjorkholm 2011, Engert 2005, Terschuren 2010, Thyss 2014, Hamaker 2014). The main findings were that clinical trials often exclude older patients (Thyss 2014). In HL, 33% of the trials exclude patients more than 65 years old (y.o.), and 39% exclude patients more than 70 y.o. (Hamaker 2014). The proportion of patients > 60 y.o. was found to be between 5-10% of the total population in clinical trials (Bjorkholm 2011) while it represents 20 to 44% in observational studies (Engert 2005). In a study evaluating the patients recorded in a HL registry, who were enrolled in optimized therapy clinical trials, 7.8% of registry patients were excluded of clinical trials due to an age > 75 (Terschuren 2010). In the same study, the proportion of patients of the registry excluded from clinical trials for the following reasons were: 7.4% for an age < 16, 5.5% for comorbidities, 1.9% for poor Performance Status (PS), and 5.8% for poor compliance (Terschuren 2010). Only 64.1% of patients of the registry were deemed eligible for optimized therapy clinical trials (Terschuren 2010).

Among the 11 studies reporting data on HL identified during this review, 9 gave information on Drivers of Effectiveness (DoE) in HL (Safar 2014, Stark 2002, Engert 2005, Brenner 2008, Bjorkholm 2011, Evens 2012, Sant 2014, Thyss 2014, Wirth 2011). Age was most frequently reported as DoE in 8 studies (Safar 2014, Stark 2002, Engert 2005, Brenner 2008, Bjorkholm 2011, Evens 2012, Sant 2014, Thyss 2014). The threshold defining older age varied across studies from 60 to 70 (Safar 2014, Stark 2002, Engert 2005, Brenner 2008, Bjorkholm 2011, Evens 2012, Sant 2014, Thyss 2014). Older age was associated with shorter Progression Free Survival (PFS) and Overall Survival (OS) (Safar 2014, Engert 2005, Brenner 2008, Evens 2012, Thyss 2014). Elderly patients were found not to be treated as aggressively as younger patients because of comorbidities and physicians’ reluctance (Stark 2002). Poorer outcome for elderly patients was deemed to be due to: conservative treatment approach, poor risk profile, treatment associated toxicity leading to higher mortality and lower dose intensity in turn leading to lower remission rate (Bjorkholm 2011). The presence of comorbidities and loss of activities of daily living were found to be a DoE for OS (Stark 2002, Evens 2012, Thyss 2014). Three studies found advanced disease stage to be a DoE as it correlates with shorter OS and PFS (Stark 2002, Engert 2005, Wirth 2011). Treatment toxicity was found to be a DoE in four studies leading to higher on-treatment mortality impacting survival and also lower remission rates as a consequence of lower dose intensity (Stark 2002, Engert 2005, Bjorkholm 2011, Thyss 2014). In addition, treatment related deaths, treatment discontinuation for toxicity, and reduced dose intensity due to toxicity were found to be more frequent in elderly patients (Stark 2002, Engert 2005, Bjorkholm 2011, Thyss 2014). Miscellaneous clinical, histological or biological factors were identified as DoE in 3 studies (Stark 2002, Wirth 2011, Safar 2014). Those were: presence of B-
symptoms, bone marrow involvement, Epstein Barr Virus (EBV) virus positivity, gammaglobulin < 10 g/l, fibrinogen > 5 g/l, high white blood cell count, which were correlated with poorer OS and/or PFS.

**Other Hematological Malignancies**

In terms of efficacy/effectiveness gaps, the presence of comorbidities, an older age and frailty or poor performance status, were found to diminish potential enrollment in RCTs and had an impact on outcomes such as response to treatment and OS in Chronic Myeloid Leukemia (CML) (Latagliata 2013), non-Hodgkin Lymphoma (NHL) (Blommeinstein 2012, Terschuren 2010), and Acute Myeloid Leukemia (AML) (Juliusson 2009, Juliusson 2012, Micol 2010).

The DoE identified in those hematological malignancies were the same as in HL or very specific to the disease and not extrapolable to HL with the notable exception of male gender in NHL (Hamlin 2013, Abrahamsson 2013, Abrahamsson 2014), and AML (Medeiros 2014). The response to treatment was found to be associated with a better OS in Chronic Lymphocytic Leukemia (CLL) (Aurran-Schleitnitz 2011), and Multiple Myeloma (Derigs 2013, Hulin 2013, Ionita 2010).

**Discussion**

In HL, age appears to be the major factor of efficacy/effectiveness gap introducing a selection bias in the recruitment of clinical trials especially when relatively aggressive treatments are tested. Age is also the major DoE; therefore exclusion of older patients could explain a good portion of the difference observed between the efficacy measured in clinical trials, and the effectiveness observed in real-life studies. However, older age is correlated with two other important DoE: presence of comorbidities and the probability to experience severe adverse events. The publications retrieved did not allow disentangling the relative weight of these factors. An element that was lacking is the distribution of the DoE according to the disease stage. Given the nature of Hodgkin Lymphoma, it is very likely that the DoE or their relative weights are different in the early stage of the disease which has generally a good survival prognosis, than in advanced disease which prognosis is notably poorer. This aspect deserves further explorations using patient individual data.

The review of literature on hematological malignancies other than HL confirmed the efficacy/effectiveness gap and DoE of HL and added only gender and response to treatment as potential DoE to be further explored in the HL dataset.

There is a need to perform additional studies with robust statistical analysis in order to bring additional information on the relative weight of these factors, and also the weight of disease stage or other factors potentially also being important DoE in HL. This would allow also giving suggestions in the design of future clinical trials on how to broaden the enrolled population to better match the real world setting.