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Can medicines development improve outcomes in asthma and chronic obstructive pulmonary disease management by driving effectiveness?

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2 **pulmonary disease management by driving effectiveness?**

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25 **Running title:** *Drivers and reasons of effectiveness*

26

27 **Journal:** Respiratory Research (Commentary article)

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29 **Availability of data and material**

30 Anonymized individual participant eCRF data from this study plus the annotated case report form,

31 protocol, reporting and analysis plan, data set specifications, raw dataset, analysis-ready dataset,

32 and clinical study report are available for research proposals approved by an independent review

33 committee. Proposals should be submitted to www.clinicalstudydatarequest.com. A data access

34 agreement will be required.

Abstract

Despite the availability of treatment guidelines and inhaled medications for asthma and chronic obstructive pulmonary disease (COPD), much remains to be done to lessen the burden of these respiratory diseases for patients. The challenge of selecting effective and efficacious drugs for patients is a key focus area for healthcare professionals. Here we discuss the concept of "drivers of effectiveness"— features of a medicine which may increase or decrease its effectiveness in the presence of real-world factors — and highlight the importance of considering these drivers in the early stages of drug development, and exploring their impact in carefully designed pragmatic trials. Using the Salford Lung studies (SLS) in asthma and COPD as an illustrative example, we discuss various features of the inhaled corticosteroid/long-acting β_2-agonist combination, fluticasone furoate/vilanterol (FF/VI), as potential drivers of effectiveness that may have contributed to the improved patient outcomes observed with initiation of FF/VI versus continuation of usual care in the UK primary care setting.

Background

The worldwide burden of asthma and chronic obstructive pulmonary disease (COPD) remains high. The global state of progress in improving health outcomes for patients with asthma has largely plateaued and there has been little advancement towards helping a large proportion of patients whose asthma remains uncontrolled [1,2]. Similarly, COPD continues to be associated with high morbidity [3,4] and according to 2016 World Health Organization estimates, COPD was the third leading cause of mortality worldwide [5]. Guidelines for the management of asthma and COPD have existed for, and evolved over, many decades. Likewise, effective medicines for asthma and COPD have been available for many years. Highly controlled efficacy studies, for example the Gaining Optimal Asthma ControL (GOAL) study [6], have demonstrated that good asthma control is possible in the majority of patients. Despite these evidence-based guidelines and medicines with proven efficacy in highly controlled clinical trials, we appear to be failing to make the headway we might expect in lessening the burden of respiratory diseases for patients.

The reasons for poor asthma control and lack of progress in asthma care have been widely described [1,2,7–10]. Haughney *et al* [10] have defined some of the obstacles to achieving good asthma control (Box 1). Similar barriers have been described for COPD [3,11].

Box 1. Obstacles to achieving good asthma control
• Wrong diagnosis • Incorrect choice of inhaler or poor technique • Lifestyle choices (e.g. smoking) • Co-morbidities (e.g. rhinitis, obesity) • Individual variation in response to treatment • Patient beliefs and adherence

While there is a strong evidence base supporting the efficacy of currently available medicines for asthma and COPD, their prescription by clinicians and use by patients is suboptimal

73 and leaves many patients at risk due to poor disease control. Incorrectly prescribed and poorly

74 utilized treatments are also costly and lead to inefficiency in healthcare systems. The challenge of

75 selecting effective and efficacious drugs for patients is a key focus area for healthcare professionals.

76   A medicine's efficacy is usually demonstrated under near-ideal conditions in double-blind

77 randomized controlled trials [DBRCTs]) [12]; such trials typically recruit highly selected patient

78 populations and operate under experimental, highly monitored and controlled conditions, which

79 may limit the generalizability of their findings to the broader disease population. Effectiveness can

80 be thought of as the interaction of a medicine's proven efficacy with factors related to patients,

81 actual medication use, and healthcare systems, which results in the effects observed in patients in

82 the everyday clinical setting (Figure 1). Abenhaim [13] has described the concept of "drivers of

83 effectiveness" — features of a medicine that may increase or decrease the effectiveness of that

84 medicine in the presence of real-world factors. These drivers of effectiveness encompass a range of

85 factors relating to the patient, the medicine, and the environment, including: (i) patient

86 acceptability, including perceived or real side effects and tolerability; (ii) the medicine's efficacy; (iii)

87 persistence of correct use of the medicine; (iv) adherence; and (v) affordability, cost-effectiveness

88 and economic factors, e.g. the price the patient may pay for medication and the patient's age. Other

89 patient-related factors and factors relating to the healthcare system and medical practice, such as

90 such as vaccination programs, self-management plans in asthma or outreach teams in COPD, may

91 also impact a medicine's effectiveness and will clearly vary in different healthcare settings.

92   Abenhaim's team and the Innovative Medicines Initiative GetReal project have suggested

93 that drivers of effectiveness should be considered early in the drug development cycle [14,15] and

94 that their impact be explored in appropriately designed studies alongside traditional DBRCTs. As

95 DBRCTs are deliberately designed to remove potential confounders, they are unlikely to allow

96 modifiers of effectiveness to be expressed. It is therefore important, as part of clinical development,

97 that drugs are tested in their intended real-world setting, with minimal intervention (i.e. mimicking

98 everyday clinical practice and preserving the usual behaviors of patients and healthcare

4

99   professionals and closely as possible) in order to evaluate the medicine's true effectiveness. The

100   inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) combination, fluticasone furoate/vilanterol

101   (FF/VI [Relvar]; GlaxoSmithKline plc.) was tested in a real-world effectiveness study program. The

102   Salford Lung Studies (SLS) in asthma and COPD evaluated the effectiveness and safety of initiating

103   once-daily inhaled FF/VI versus continuing usual maintenance inhaler therapy (usual care [UC]) in

104   the UK primary care setting. UC comprised a wide variety of inhaled and oral medicines as

105   prescribed by each individual general practitioner (GP) taking part in the study and was not

106   determined by protocol — a major difference compared with typical DBRCTs. The SLS designs and

107   results have been published previously [16–20]. These open-label, pragmatic, randomized,

108   controlled effectiveness trials demonstrated the benefits of initiating FF/VI versus continuing UC in

109   terms of their respective primary endpoints of improvements in asthma control and reduction in

110   COPD exacerbations [19,20]. The studies were designed to enable GPs to function as study

111   investigators, with changes in treatment during the study permitted based on their clinical opinions.

112   The results of the SLS raise the questions of what features were driving the improved

113   effectiveness observed for FF/VI versus UC, and how could those drivers of effectiveness help to

114   address some of the obstacles for improving care for patients with asthma and COPD?

115

116   **Potential drivers of effectiveness in asthma and COPD**

117   FF/VI delivered via the ELLIPTA dry powder inhaler was designed as an improvement over

118   fluticasone propionate/salmeterol delivered via the Diskus inhaler. An overview of factors thought

119   to be important in driving clinical effectiveness is presented in Figure 2. Various features of FF/VI

120   could potentially have improved effectiveness and patient outcomes with initiation of FF/VI versus

121   continuation of UC in the SLS, as discussed below.

122

123   **Once-daily dosing**

124   Patient adherence with inhaled medications for the treatment of asthma and COPD is low [21,22] for

125   reasons including patient beliefs, side effects, dosing frequency, and poor inhaler technique [21–23].

126   In studies of adherence in the real-world setting, adherence rates have been reported to be as low

127   as 10% and typically between 20–40% [24–28].

128   Once-daily treatment administration has the potential to encourage/increase adherence

129   compared with twice-daily administration, as evidenced in medications for asthma and other

130   indications [29–31]. FF/VI was the first once-daily inhaled ICS/LABA combination to be broadly

131   available worldwide. In the SLS, adherence was assessed using the Medication Adherence Report

132   Scale for Asthma (MARS-A) questionnaire and patients' prescription records were accessed through

133   their electronic case report forms. The MARS-A was used to gather patients' patterns of medication

134   use (e.g. "I only take it when I need it"), and the number of prescriptions issued was used to

135   estimate the proportion of days covered (PDC) by study medication as a surrogate for treatment

136   adherence. Both methods have their limitations: the MARS-A is a validated questionnaire to assess

137   self-reported adherence, but self-reported behavior does not always reflect actual behavior, such as

138   unintentional non-adherence. Furthermore, the measure captures patients' general tendencies of

139   how they take their medication, not actual adherence *per se*. The use of prescribing data has

140   considerable limitations in assessing adherence, as it only records the number of prescriptions

141   issued, and not the number dispensed to, or actually used by, patients. Nevertheless, in SLS asthma,

142   the reported mean PDC was 82.3% for FF/VI and 78.2% for UC and in SLS COPD was 85.0% for FF/VI

143   and 82.4% for UC [32,33]. As planned, no statistical testing has been conducted on these data.

144   Further assessment of adherence to FF/VI through electronic monitoring devices will aid better

145   understanding of this driver of effectiveness [34–37].

146

147   **Rapid onset and long duration of action of the active molecules**

148   The rapid onset of action of a medication may result in a perceived benefit to the patient that may

149   encourage treatment adherence [38]. A longer duration of action beyond the licensed dosing

150   interval may mean that the medicine is more "forgiving" of the non-adherence commonly

151   encountered in everyday practice (including irregular dosing and use) [39,40]. The onset and

152   duration of action of FF/VI has been assessed in asthma. Studies evaluating the bronchodilator

153   effects of FF/VI using serial lung function measures in asthmatic patients have demonstrated an

154   onset of action as early as 15 minutes [41] and a 72-hour duration of bronchodilation after a single

155   dose [42]; slower in onset than formoterol (within minutes [43,44]) and longer in duration of action

156   than formoterol or salmeterol (at least 12 hours) [43–45]. Bardsley *et al* examined the duration of

157   airway anti-inflammatory action of FF/VI by serially measuring fractional exhaled nitric oxide (FeNO)

158   over a 14-day treatment period with FF/VI and over 21 days following cessation of therapy. Full

159   suppression of FeNO in asthma was estimated to last for up to 3 days, with effective suppression

160   continuing for up to 18 days, and improvements in forced expiratory volume in 1 second and peak

161   expiratory flow lasting for 3–4 days after cessation of treatment [46]. While there are limited

162   comparative data on the duration of anti-inflammatory action for ICS, separate studies in patients

163   treated with budesonide have reported FeNO return to baseline values within 7 days of cessation of

164   treatment [47].

165

166   **Device features and design**

167   Effective drug delivery systems enable the controlled introduction of a medicine into the body, while

168   also improving drug efficacy and safety [48]. The dosage form and device can directly impact on

169   treatment success and patient adherence [48]. Critical errors — those that can be defined as errors

170   resulting in limited or no medication being delivered to the lung — have been associated with major

171   impacts on respiratory symptoms and healthcare consumption [49,50]. The ELLIPTA inhaler has been

172   shown to be superior to other commonly used inhalers for the administration of ICS/LABA

173   medicines, in terms of patient preference for its design features of dose counter, ease of use, and

174   dosing regimen [51]. Furthermore, it has been shown that fewer patients make critical errors with

175   the ELLIPTA inhaler compared with a range of other ICS/LABA inhalers, and that the ELLIPTA inhaler

176 requires less teaching time than other inhalers [52]. In studies evaluating the dose delivery achieved

177 through ELLIPTA, patients received a dose close to the label claim with inspiratory flow rates of 30

178 L/min and above 30 L/min peak inspiratory flow rate. Furthermore, studies have shown that asthma

179 and COPD patients across a range of disease severities achieved a flow of 43 L/min or above [53]. In

180 everyday practice, a simple inhaler that requires less time to teach the correct technique, is easy to

181 use, has a low potential for patients to make critical errors, delivers adequate dose across a broad

182 range of inspiratory flow rates, and is preferred by patients, will be a positive driver of effectiveness

183 since there will be greater confidence that the medication has been optimally delivered.

184

185 **Tolerability**

186 A theoretical consequence of some drivers of effectiveness is that, while the likelihood of correct

187 and adequate dosing increases, the benefits in terms of positive outcomes might be outweighed by

188 an increased risk of side effects. Tolerability and adverse events reported in phase lll clinical studies

189 of FF/VI in patients with asthma and COPD were similar to those seen with the fluticasone

190 propionate/salmeterol combination [54–56]. In the SLS, serious adverse event rates were very

191 similar for FF/VI and UC [19,20]. Modeling studies have suggested that FF may have a better

192 therapeutic index than other inhaled steroids [57].

193

194 **Discussion**

195 Asthma and COPD guidelines and regulatory and payer frameworks have long favoured DBRCTs as

196 constituting the highest level of evidence [3,58]. Although Cochrane highlighted the importance of

197 understanding the effectiveness of medicines back in 1972 [12], his enthusiasm has not been

198 broadly shared. Pragmatic real-world study designs have not been universally adopted and drug

199 development has instead continued to focus on evaluating efficacy within highly controlled trials in

200 highly selected patient populations. As a result, we are left struggling to assess the external validity

201 of the results of such studies and medicine development programs. As well designed effectiveness

202 studies are undervalued due to their pragmatic design features, the overriding focus on efficacy

203 evaluation is likely to have hampered the implementation of drivers of effectiveness early in drug

204 development processes.

205 The SLS were world-first, pragmatic, randomized, controlled trials conducted in the routine

206 UK clinical practice setting to evaluate a pre-licensed inhaled medicine [16]. The trials were open-

207 label to maintain their pragmatic design; however, this meant open-label for patients, GPs,

208 pharmacists, other healthcare providers, and most of the study team. This could have introduced

209 bias, particularly as FF/VI would have been either unlicensed or newly licensed while the studies

210 were ongoing. In an attempt to minimise this bias, sponsor study team members who were involved

211 in the development of the analysis plan and the actual data analyses were blinded to patients'

212 individual therapies up until the formal unblinding of the studies, which occurred after the databases

213 had been finalized. The SLS exemplify that by designing drivers of effectiveness into a medicine, the

214 medicine alone can improve patient outcomes compared to other medications in the same drug

215 class.

216 It is difficult to assess which components of the composite drivers of effectiveness play the

217 biggest part in improving patient outcomes. Moreover, these drivers are likely to reinforce one

218 another, whereby the physical features of the medicine are improving outcomes and, thus, patient-

219 perceived benefits, which in turn may enhance the belief that the medicine is making a difference.

220 For example, a longer duration of action of a medicine is likely to mitigate any sub-optimal

221 adherence, thus altering the impact of the latter on actual and perceived symptom control. Likewise,

222 an easy-to-use inhaler would enhance the likelihood that the medicine is inhaled correctly, which

223 would increase its effectiveness, as measured and as perceived by patients. We suggest that further

224 work in this field should be pursued for guiding drug developers to design better medicines. We also

225 suggest that regulators, guideline writers, and payers should seek to understand the now well-

226 established concept of effectiveness and build it into their frameworks.

227   Traditional DBRCTs are deliberately designed to remove potential confounders such as

228   device and patient preference, and thus are unlikely to allow modifiers of effectiveness to be

229   expressed. Such trials rely on highly selected patient populations chosen for their compliance with

230   treatment and study visits, who are typically socially stable, and have high adherence and near-

231   perfect inhaler technique; these patients are not representative of patients seen in everyday clinical

232   practice. Trials such as the SLS show that patients in primary care, recruited with minimal exclusion

233   criteria, can participate in a randomized controlled trial and yield data that complement the data

234   obtained in traditional efficacy DBRCTs.

235   Currently, we may be ignoring a crucial aspect of medicine assessment and, therefore,

236   denying patients the opportunity for more effective therapies, while also discouraging effectiveness

237   and patient-focused medicine development.

238

239   **Conclusions**

240   Evidence suggests that it is possible to design medicines to include a composite of features that can

241   drive effectiveness. Improving a medicine's effectiveness can provide a meaningful impact on

242   patient outcomes, which can be demonstrated through appropriately designed pragmatic clinical

243   trials. It is time to reconsider evidence hierarchies and bring more external validity to them. This is

244   ultimately likely to benefit patients through encouraging patient-focused drug development, which

245   includes consideration of the drivers of effectiveness and making more effective medicines available

246   to patients.

247

248

249   **List of abbreviations**

250   COPD: chronic obstructive pulmonary disease; DBRCTs: double-blind randomized controlled trials;

251   FeNO, forced exhaled nitric oxide; FF/VI: fluticasone furoate/vilanterol; GP, general practitioner; ICS:

252   inhaled corticosteroid; LABA: long-acting β_2-agonist; MARS-A: Medication Adherence Report Scale

253   for Asthma; PDC: proportion of days covered; SLS: Salford Lung Studies; UC: usual care.

254

255   **Declarations**

256   **Ethics approval and consent to participate**

257   The Salford Lung Study protocols were approved by the National Research Ethics Service Committee

258   North West, Greater Manchester South (approval numbers 12/NW/0455 and 11/NW/0798). All

259   patients provided written informed consent for participation.

260

261   **Consent for publication**

262   All authors have contributed to the writing and/or critical review of this manuscript and all have

263   approved the final version for submission for publication.

264

265   **Availability of data and material**

266   Anonymized individual participant data from this study plus the annotated case report form,

267   protocol, reporting and analysis plan, data set specifications, raw dataset, analysis-ready dataset,

268   and clinical study report are available for research proposals approved by an independent review

269   committee. Proposals should be submitted to www.clinicalstudydatarequest.com. A data access

270   agreement will be required.

271

272   **Competing interests**

300   Trade marks are the property of their respective owners.

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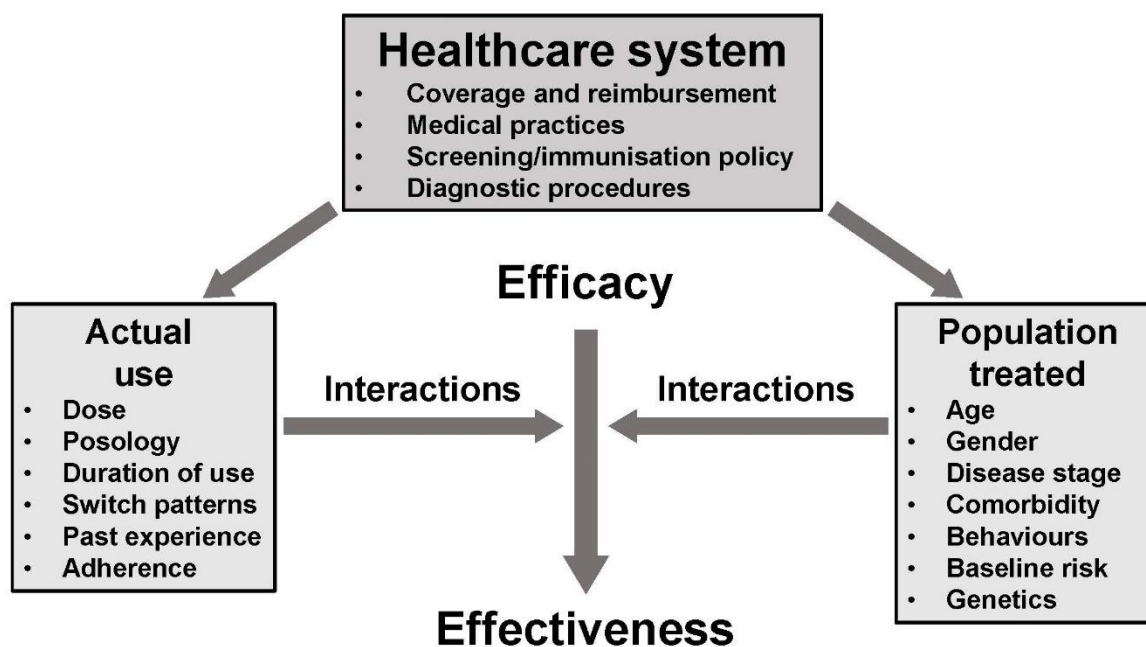488   report-V1.3-002.pdf. Last accessed 10 June 2019.

489

490　**Figure legends**

491

492　**Figure 1 Drug efficacy, factor interactions and effectiveness.**

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494　**Figure 2 Main drivers of clinical effectiveness.**

Figures

496   **Figure 1 Drug efficacy, factor interactions and effectiveness.**

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498   Reproduced with permission from Prof. Lucien Abenhaim, Relativity in the assessment of Medicines

499   Symposium, London, 2010.

500   **Figure 2 Main drivers of clinical effectiveness.**

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