*DISCLAIMER – The data regarding numbers of inhalers purchased/used and their cost provincially and at Island Health are confidential and have been edited with fictional numbers to illustrate an example analysis. We used the published List prices (not contract prices) for the inhaler devices. The analysis herein utilizes the carbon footprint of the high volume HFA salbutamol device.

Fictional numbers / List Prices used for example analysis:
Salbutamol MDI baseline annual purchasing data provincially = 100,000 devices
Salbutamol MDI baseline annual purchasing data Island Health = 25,000
Salbutamol MDI cost = $6.50 per inhaler
Salbutamol DPI cost = $10.72 per inhaler
Terbutaline baseline annual purchasing data provincially = 120 devices
Terbutaline DPI cost = $10.19 per inhaler

British Columbia Health Authorities Pharmacy and Therapeutics (BCHA P&T)
Formulary Drug Review
June 23, 2022

terbutaline sulfate dry powder for oral inhalation

Prepared by the BCHA Pharmacy & Therapeutics Drug Review Subcommittee
Lead Reviewers: Carly Webb and Aaron Tejani

*DISCLAIMER – The data regarding numbers of inhalers used and their cost provincially and at Island Health are confidential and have been edited with fictional numbers to illustrate an example analysis.

Table of Contents

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1. EXECUTIVE SUMMARY

List of acronyms used in this report
CFC: chlorofluorocarbon
CO_2e: carbon dioxide equivalent
COPD: chronic obstructive pulmonary disease
DPI: dry powder inhaler
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
GHG: greenhouse gas
GWP: global warming potential
HFA: hydrofluoroalkane
HFC: hydrofluorocarbon
ICS: inhaled corticosteroid
LCA: life cycle assessment
PEF: peak expiratory flow
pMDI: pressurized metered dose inhaler
SABA: short acting beta agonist
SAMA: short acting muscarinic antagonist
SMI: soft mist inhaler
tCO_2e: tonnes of carbon dioxide equivalent (1 metric tonne = 1000 kg)

Drug: terbutaline sulfate dry powder for oral inhalation (BRICANYL TURBUHALER)

Indication requested: symptomatic relief of bronchial asthma and for relief of reversible bronchospasm which may occur in association with bronchitis and emphysema and COPD

Formulary Alternatives (if applicable): salbutamol respiratory (inhalation) aerosol metered dose, powder, and solution

Pharmacology / Mechanism of Action (include Health Canada indication):
BRICANYL TURBUHALER (terbutaline sulfate) produces bronchodilation by stimulation of the β2-adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of muscle fibers. This action is manifested by an increase in pulmonary function as demonstrated by Forced Expiratory Volume in 1 second (FEV_1) measurements. BRICANYL TURBUHALER also produces a decrease in airway and pulmonary resistance.[1]

***DISCLAIMER – The data regarding numbers of inhalers used and their cost provincially and at Island Health are confidential and have been edited with fictional numbers to illustrate an example analysis.**

Table 1. BC Health Authorities Budget Impact Analysis*

Products	Cost in FY 2020-21	New cost if 1.3% switch to terbutaline	New cost if 50% switch to terbutaline
salbutamol 100 mcg/puff pMDI *Ventolin HFA, generics*	$650,000*	$641,550*	$325,000*
terbutaline 500 mcg/puff DPI *Bricanyl Turbuhaler*	$1,222.80*	$14,469.80*	$510,722.80*
Total Annual Cost (all health authorities)	**$651,222.80* (cost in 2020-21)**	**$656,019.80* (an increase of $4,797* per year)**	**$835,722.80* (an increase of $184,500* per year)**

Table 2. BC Health Authorities Environmental Impact Analysis*

Products	tCO_2e in FY 2020-21	New tCO_2e if 1.3% switch to terbutaline	New tCO_2e if 50% switch to terbutaline
salbutamol 100 mcg/puff pMDI *Ventolin HFA, generics*	2,500*	2,467*	1,250*
terbutaline 500 mcg/puff DPI *Bricanyl Turbuhaler*	0.1*	1*	35*
Total Annual Cost (all health authorities)	**2,500* (tCO_2e in 2020-21)**	**2468* (a decrease of 32* tCO_2e per year)**	**1285* (an decrease of 1215* tCO_2e per year)**

With presumably similar efficacy and safety, terbutaline contributes less greenhouse gas emissions (↓ 24* kg CO_2e/inhaler) but comes at an increased cost (↑ $3.69*/inhaler) compared to salbutamol pMDI. Compared to salbutamol DPI (VENTOLIN DISKUS), terbutaline has presumably similar efficacy and safety, and similar greenhouse gas emissions, but comes at a lower cost.

If prescribing practice does not significantly change from current community patterns, adding terbutaline to formulary will have a negligible budgetary or carbon footprint impact. However, if prescribing culture moves toward more DPI use, it is estimated up to 50% of salbutamol pMDI use could be replaced by terbutaline DPI at an increased cost to health authorities of $184,500* per year. A 50% switch rate would mitigate an estimated 1215* tonnes of CO_2e (tCO_2e) emissions per year.

CADTH Recommendation: N/A

B.C. PharmaCare Decision: Regular Benefit

Clinical Review Summary:

Focused Clinical Question(s):

1. Does terbutaline DPI (BRICANYL TURBUHALER) offer environmental impact advantages in terms of global warming potential (GWP), or other measures, over salbutamol pMDI?
2. In adult patients with asthma or COPD, does terbutaline DPI (BRICANYL TURBUHALER), have significant differences in efficacy or safety compared to salbutamol pMDI?

***DISCLAIMER – The data regarding numbers of inhalers used and their cost provincially and at Island Health are confidential and have been edited with fictional numbers to illustrate an example analysis.**

Discussion from Review: (highlighting any controversies or particularly notable points for discussion/debate)

The available environmental evidence has consistently shown that pMDIs contribute far more to greenhouse gas emissions compared to DPIs, due to their HFC propellants. However, most of the source data is not available in the public domain and comes from industry who may have a financial incentive to move toward DPI use. DPIs also performed worse on other outcomes such as marine eutrophication, photochemical oxidants formation, and fossil depletion. In addition, products and manufacturing processes may different between countries, and none of the environmental impact studies were performed in Canada.

Very limited clinical evidence exists directly comparing inhaled terbutaline to inhaled salbutamol. The available evidence is over 20 years old and may have limited generalizability to our current population due to changes in asthma management since that time.

Terbutaline DPI (BRICANYL TURBUHALER) would be the best choice of a SABA DPI for BCHAs to carry as it is also a benefit with BC PharmaCare, allowing for continuity of care, and a less expensive option than salbutamol DPI (VENTOLIN DISKUS) which is not a PharmaCare benefit.

Recommendation:

A.	Should this drug be added to Formulary? [Specify: Formulary, Formulary-Restricted (include restrictions) or Excluded]	Formulary
B.	What is the budget impact should this be added to the Formulary?	An estimated increased cost of $4,797* to $184,500* depending on uptake
C.	If added, is there risk in inappropriate use of this agent and if so, outline any concerns.	No
D.	If added, should any existing formulary agent be deleted from the Formulary?	Yes, salbutamol DPI (VENTOLIN DISKUS) should be removed due to low usage and to align with PharmaCare coverage
E.	If added, are there any particular implementation issues which need to be addressed (e.g., staff education, staff communication)?	Staff education on new inhaler device may be beneficial
F.	If added, does this medication need to be added to the provincial hazardous drug classification?	No
G.	If added, should utilization of this drug be monitored?	No

BCHA P&T Decision: (post P & T) (date)

Reason for Decision: (post P & T)

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2. FORMULARY REQUEST

a) Generic/brand name

terbutaline sulfate dry powder for oral inhalation (BRICANYL TURBUHALER)

b) Dosage forms/strengths[1]

BRICANYL TURBUHALER (terbutaline sulfate) is a multidose, inspiratory flow driven metered dose dry powder inhaler that is supplied in one strength: 0.5 mg/dose. This corresponds to a delivered dose (the dose leaving the mouthpiece) of 0.4 mg terbutaline sulfate.

c) Pharmacology, mechanism of action[1]

BRICANYL TURBUHALER (terbutaline sulfate) produces bronchodilation by stimulation of the β2-adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of muscle fibers. This action is manifested by an increase in pulmonary function as demonstrated by Forced Expiratory Volume in 1 second (FEV_1) measurements. BRICANYL TURBUHALER also produces a decrease in airway and pulmonary resistance.

d) Manufacturer and competitors listed

salbutamol respiratory (inhalation)

- AIROMIR HFA 100 mcg MDI (Bausch Health)
- VENTOLIN HFA 100 mcg MDI (GlaxoSmithKline)
- VENTOLIN DISKUS 200 mcg DPI (GlaxoSmithKline)
- salbutamol sulfate HFA 100 mcg MDI (multiple generics)

e) Health Canada approved indication(s)[1]

BRICANYL TURBUHALER (terbutaline sulfate) is indicated as a bronchodilator for the symptomatic relief of bronchial asthma and for relief of reversible bronchospasm that may occur in association with bronchitis and emphysema.

Pediatrics (≥6 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of BRICANYL TURBUHALER in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. BRICANYL TURBUHALER is not recommended for children under the age of 6.

Original notice of compliance date: 2000-05-01

f) Indication(s) requested/doses/dose adjustments needed

Symptomatic relief of bronchial asthma and for relief of reversible bronchospasm that may occur in association with bronchitis and emphysema and COPD.

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g) Origin of request

The BC Drug Review Subcommittee (DRS) initiated the request after hearing concerns about the environmental impact of aerosol metered dose inhaler devices from several clinicians.

h) Current BC PharmaCare coverage status

- terbutaline DPI (BRICANYL TURBUHALER): Regular benefit
- salbutamol pMDI (VENTOLIN HFA, generics): Regular benefit
- salbutamol DPI (VENTOLIN DISKUS): Non-benefit

3. BACKGROUND

a) Environmental impacts of inhalers

A British Thoracic Society position statement concludes, "Healthcare professionals have a duty to protect and promote the health of patients and the public, and climate change currently represents the greatest global threat to public health. Sustainable use of precious environmental resources is therefore the responsibility of all healthcare professionals, delivering benefits now as well as protecting the health of future generations."[2]

The health impacts of the climate crisis are causing increasing concern. A child born today will experience a world 4°C warmer than the pre-industrial average. Health impacts of climate change include failing crops and undernutrition, infectious diseases, heatwave exposure, and mortality related to natural disasters.[3] Exposure to air pollution will increase their risk of respiratory and cardiovascular disease.[3] If we are to avoid the worst effects of the climate crisis, then all sectors of society must dramatically reduce greenhouse gas emissions.

The National Health Service (NHS) in England has conducted significant research into the contribution of the healthcare sector to carbon emissions. In England, seven percent of all emissions are from healthcare (26.6 Mt of 370 Mt CO_2e annually). Pharmaceuticals account for 3.6 Mt and pressurized metered-dose inhalers (pMDIs are the largest single contributors to the pharmaceutical-related greenhouse gas (GHG) emissions. The overall contribution of inhalers to the UK's GHG emissions is around 0.3%. Although this percentage appears of be small, it is equivalent to the annual GHG emission from 610,000 diesel cars in the UK.[4] The NHS goal is a 50% cut in the carbon footprint of inhalers to reach the 2030 NHS carbon reduction targets.[5]

Pressurized metered-dose inhalers (pMDIs) like salbutamol pMDI rely on the driving force of propellants, which comprise the bulk of any pMDI formulation, to atomise droplets containing drug and excipients for deposition in the lungs. In the past, chlorofluorocarbons (CFC) were used as propellants in pMDIs. These ozone-depleting chemicals were banned by the ratification of the Montreal Protocol on Substances that Deplete the Ozone Layer in 1987.[4] An industry-wide transition occurred from CFC to hydrofluorocarbon (HFC) propellants, also known as hydrofluoroalkane (HFA). HFC-134a is the propellant now used in most pMDIs, with HFC-227ea used to a lesser extent. This move had ozone-related benefits as well as an order of magnitude reduction in the global warming potential (GWP) associated with propellant use.[4] However HFCs are still potent greenhouse gases. HFC-134a is 1300 times more potent than CO_2 as a greenhouse gas and HFC-227ea 3350 times more potent.[3]

In 2016, 170 countries adopted the Kigali Amendment to the Montreal Protocol with a goal of phasing down the use of HFCs by 80-85% by 2042. This target is expected to reduce the emission of CO_2e by 70 billions tons by 2050, avoiding up to a 0.5°C global temperature rise by 2100, as well as protecting the ozone layer. The majority of HFC usage is in the refrigeration and air conditioning sector, but healthcare is also a target sector for HFC phase-down by the UN.[6]

Dry powder inhalers (DPIs) and soft-mist inhalers (SMIs) do not contain a propellant and thus their carbon footprint is mainly dependent on the raw materials and manufacturing process.[4] The usage of pMDIs versus DPIs varies significantly between countries (e.g. 34% in Japan and 88% in the US).[7] This may be a result of differing health policies, costs, insurance issues, commercial availability, and prescriber and patient preferences. There is no consensus on the best inhaler for all patients. Some studies advocate that patients can use pMDIs effectively and others advocate that patients are able to use DPIs more effectively.[7] The most appropriate inhaler should be identified for each patient to ensure optimal care. For pMDIs the patient must coordinate the actuation of the spray with inhalation, for SMIs the relatively long duration of spray requires a slow inhalation, whilst for DPIs, an optimal dose of drug to the lungs requires a deep and forceful inhalation. There are groups of patients who struggle to generate sufficient inspiratory flows to get adequate delivery from a DPI.[7] Thus, the very young, very old, and very ill should not be switched to DPIs.

To compare the impact on climate change between different products, the carbon footprint can be calculated throughout the life cycle of the product, including: raw materials, production, transport, use and waste disposal.[4] Carbon dioxide equivalent (CO_2e) is the unit for comparing the radiative forcing of a greenhouse gas (GHG) to that of CO_2. The mass of a GHG is converted into CO_2e by multiplying by the corresponding global warming potential (GWP).[8]

There have been different options proposed to reduce GHG emissions from pMDIs, including:[3]

- Prevent need for inhalers through smoking cessation, reduced exposure to air pollution, or improved management of respiratory conditions
- Improve inhaler technique and spacer use
- Use alternative devices such DPIs or nebulizers
- Reduce the amount of propellant used per dose (up to drug companies)
- Use different propellants with a lower GWP (current area of research)
- Reduce wastage
- Reduce inappropriate prescribing
- Increase recovery and recycling rates for used inhalers
- Appropriate disposal (incineration of pMDIs converts the HFCs into products with lower greenhouse effects)

b) Disease state overview[9,10]

Asthma is a heterogeneous disease characterized by chronic airway inflammation resulting in airflow limitation. Patients typically present with a history of wheeze, shortness of breath, chest tightness and cough. The symptoms vary over time and with intensity as inflammation and airflow limitations worsen or improve. Goals of therapy are to prevent asthma-related mortality, prevent exacerbations, maintain asthma control, and improve quality of life. Targets for asthma control are occurrence of symptoms < 3 days per week or use of reliever < 3 doses per week.

Chronic obstructive pulmonary disease (COPD) is a systemic disease largely caused by smoking and characterized by progressive, partially reversible airway limitation; systemic manifestations (e.g., altered nutrition); and increasing frequency and severity of exacerbations. Goals of therapy are to prevent

disease progression, decrease or eliminate breathlessness, improve exercise tolerance, reduce exacerbations, improve quality of life, and reduce mortality.

c) Available treatments[9,10]

Short-Acting Bronchodilators:

- salbutamol pMDI, DPI, and nebules (VENOTLIN HFA, DISKUS)
- terbutaline DPI (BRICANYL TURBUHALER)
- ipratropium pMDI, and nebules (ATROVENT HFA)
- ipratropium/salbutamol SMI and nebules (COMBIVENT RESPIMAT)

d) Key outcome measures

Asthma: Mortality, exacerbations, change in asthma control, lung function (FEV_1, FEV_1/FVC ratio), change in medication use, Emergency Department (ED)/hospital visits, quality of life.[11]

COPD: Mortality, exacerbations, lung function (FEV_1, lung volumes), exercise capacity, dyspnea measurement scales, quality of life.[12]

e) Relevant clinical practice guideline recommendations

Recommendations on the choice of reliever inhaler and choice of inhaler device from key guidelines are summarized below.

<u>2021 GINA Recommendations</u>[13]

- Track 1 (reliever is inhaled corticosteroid [ICS]-formoterol, typically budesonide-formoterol [SYMBICORT]):
    - The preferred approach by GINA as it reduces the risk of severe exacerbations compared with using a SABA reliever.
    - Low dose ICS-formoterol used as needed for symptom relief, and in Steps 3-5 they take ICS-formoterol as regular daily treatment.
- Track 2 (reliever is a SABA):
    - Alternative if Track 1 is not possible, or is not preferred by a patient with no exacerbations on their current therapy. In Step 1 the patient takes a SABA and a low dose ICS together for symptom relief, in Steps 2-5 the reliever is a SABA.
- Choice of device:
    - Delivery of SABA via a pMDI and spacer or a DPI leads to a similar improvement in lung function as delivery via nebulizer. However, patients with acute severe asthma were not included in these studies.
    - No "perfect" inhaler – patients can have problems using any inhaler device. Consider medication options, available devices, patient skills, and cost. Encourage the patient to participate in the choice.
    - pMDI with spacer recommended for children 5 years old and younger.

<u>2020 GOLD Guidelines</u>[14]

- Choice of reliever:
    - Short-acting beta agonist choices include fenoterol, levalbuterol, salbutamol, and terbutaline.
    - Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms (Evidence A).

  - Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms (Evidence A).

- Choice of device:
  - Randomized controlled trials have not identified superiority of one device/formulation. However, patients included in these trials are usually those who master inhalation technique and receive proper education and follow-up, and therefore may not be reflective of normal clinical practice.
  - The choice of inhaler device must be individually tailored and will depend on access, cost, prescriber, and most importantly, patient's ability and preference.

Other organizations (regarding environmental concerns):

- The National Institute for Health and Care Excellence (NICE) has published a Patient Decision Aid on asthma inhalers that lists carbon footprint as a key criterion in the choice of an inhaler, with DPIs favored[15]
- The British Thoracic Society (BTS) has published a position statement that recommends that the DPI class be prioritized over pMDIs, when patients are able to use them safely, in order to reduce the environmental impact of inhaler prescribing.[2] The BTS also calls for optimizing patients' inhaler technique, plus expanding recycling and disposal schemes.

f) Patient Perspective

A survey conducted in the UK found that 80% of patients rated the ease-of-use as important or very important consideration when changing inhalers. The 'cost' and 'carbon footprint' of the inhaler were equally important to patients (3.4 out of 5); only 14% of patients indicated that carbon footprint was of no importance to them.[16]

4. CLINICAL REVIEW QUESTION(S)

a) Focused clinical question

Question 1:
Does terbutaline DPI (BRICANYL TURBUHALER) offer environmental impact advantages in terms of global warming potential (GWP), or other measures, over salbutamol pMDI?

Question 2:
In adult patients with asthma or COPD, does terbutaline DPI (BRICANYL TURBUHALER), have significant differences in efficacy or safety compared to salbutamol pMDI?

b) Hierarchy of environmental outcomes

Creating a hierarchy of environmental outcomes requires unique considerations, compared to creating a hierarchy of health outcomes.

- Environmental impact scores across different categories can be created using characterization factors.[17] There are two mainstream ways of deriving characterization factors: at midpoint or endpoint. Characterization factors at the endpoint level correspond to three areas of protection: human health, ecosystem quality and resource scarcity (see Figure 1).

- Interpreting environmental impact factors requires a values-based assessment with cultural perspectives. An individualist method assesses the short term with optimism that technology can avoid many problems in the future (time horizon of 20 years). A hierarchist approach is a consensus model most often encountered in scientific models (time horizon 100 years). An egalitarian approach is long term, based on precautionary principal thinking (time horizon 1,000 to infinite years).[17]
- Environmental impact factors can also be broken down into whether they will have a regional or global impact.

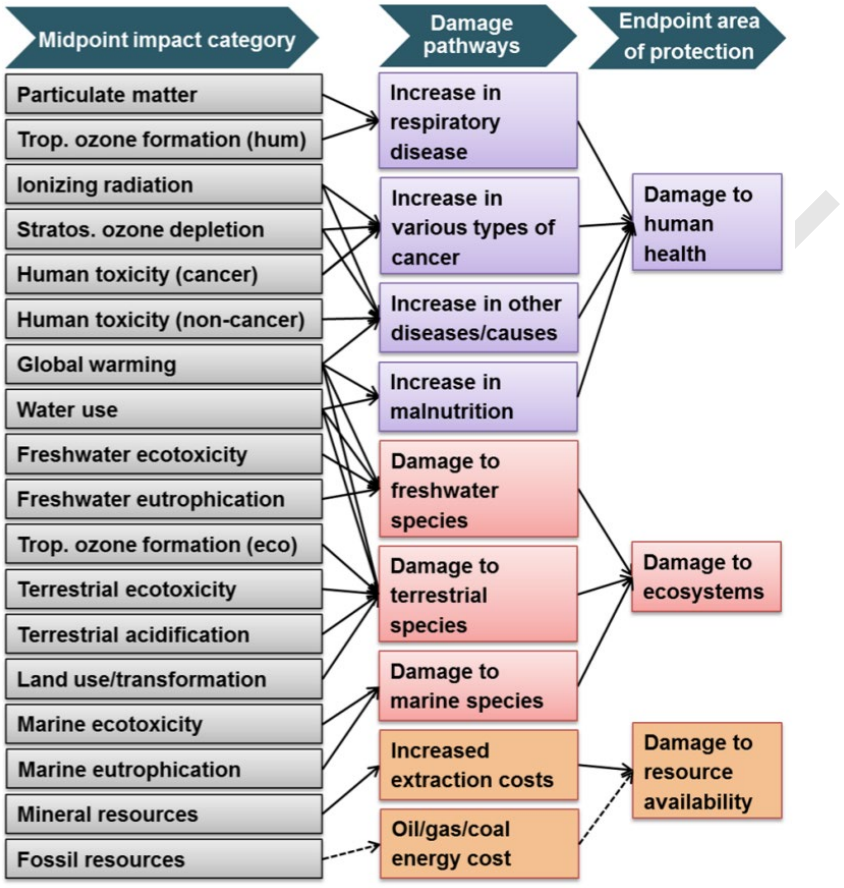


Figure 1. Overview of the impact categories that are covered in the ReCiPe 2016 methodology[17]

The European Union Joint Research Centre (JRC) has developed a model to weigh the value of the different environmental impact factors. However, they report that there is no universal consensus on a weighting scheme and it is not mainly based on natural science but inherently involves value choices that will depend on policy, cultural and other preferences. The JRC's weighting model is based on a hybrid evidence and judgement-based weighting set. Criteria included spread of impact, time span to general an impact, reversibility, level of impact compared to planetary boundary, effect on human health, effect on ecosystem quality, and effect on resources availability.

As shown in Figure 2 below, the category of climate change was ranked as most concerning environmental impact factor.[18]

Based on the JRC model, the environmental impact category of climate change will be used as the most important factor, and therefore the primary outcome to be assessed in this review. This is also known as global warming potential (GWP) and is measured in kg of CO_2 (or equivalent) to air. Other environmental impacts will be considered as secondary outcomes.

	Aggregated weighting set	Robustness factors	Intermediate Coefficients	Final weighting factors (incl. robustness)
	(A)	(B)	C=A*B	C scaled to 100
Climate change	12.90	0.87	11.18	**21.06**
Ozone depletion	5.58	0.60	3.35	**6.31**
Human toxicity, cancer effects	6.80	0.17	1.13	**2.13**
Human toxicity, non-cancer effects	5.88	0.17	0.98	**1.84**
Particulate matter	5.49	0.87	4.76	**8.96**
Ionizing radiation, human health	5.70	0.47	2.66	**5.01**
Photochemical ozone formation, human health	4.76	0.53	2.54	**4.78**
Acidification	4.94	0.67	3.29	**6.20**
Eutrophication, terrestrial	2.95	0.67	1.97	**3.71**
Eutrophication, freshwater	3.19	0.47	1.49	**2.80**
Eutrophication, marine	2.94	0.53	1.57	**2.96**
Ecotoxicity freshwater	6.12	0.17	1.02	**1.92**
Land use	9.04	0.47	4.22	**7.94**
Water use	9.69	0.47	4.52	**8.51**
Resource use, minerals and metals	6.68	0.60	4.01	**7.55**
Resource use, fossils	7.37	0.60	4.42	**8.32**

Figure 2. The recommended weighting set, robustness factors and final weighting factors for all midpoint impact categories[18]

c) Hierarchy of health outcomes - *See Appendix 1. Hierarchy of Outcomes*

d) Hierarch of evidence - *See Appendix 2. Hierarchy of Evidence*

5. CLINICAL REVIEW METHODS & RESULTS

One reviewer conducted the literature searches, screened titles and abstracts, and retrieved full text versions for further review and selection according to the below criteria.

Question 1 (environmental outcomes):

a) Search Strategy - *See Appendix 3. Search Strategy*

- Data sources: Canadian Agency for Drugs & Technologies in Health (CADTH), Cochrane Database of Systematic Reviews, MEDLINE, Embase, in addition to hand search of review article reference lists. Search was conducted Jan 27, 2022.
- Search terms: Administration, Inhalation; Adrenergic beta-Agonists/ad [Administration & Dosage]; Asthma/dt [Drug Therapy], "Nebulizers and Vaporizers"; Pulmonary Disease, Chronic Obstructive/dt [Drug Therapy]; Carbon Footprint; Greenhouse Effect; Greenhouse

Gases; Global Warming

b) Publication restrictions: articles, reviews (excluded conference abstracts, letters)

c) Study selection criteria: any original research that compared the environmental impact of pMDI to DPI

d) Trial Flow Diagram - *See Appendix 4. Trial Flow Diagram*

e) Trial summaries - *See Appendix 5. Trial Overview & Results Tables*

All five studies that met the inclusion criteria for the review of environmental impact of pMDIs versus MDIs were conducted in the UK and/or Europe.[4,19–22] Study methodology varied. A few studies included scenarios where HFC-152a would be used as an alternative propellant in pMDIs, however this is an investigational product and no inhalers currently on the market in Canada use this propellant. Data sources for calculating GWP were from either industry, proprietary databases, published literature, or a combination. Table 3 provides a summary of results for the GWP of pMDIs and MDIs. Results were overall consistent between studies, with pMDIs having a 17 to 49 times higher GWP compared to DPIs.

Table 3. Summary of study results comparing GWP of pMDIs versus DPIs

Study	pMDI^ GWP per inhaler (kg CO_2e)	DPI GWP^ GWP per inhaler (kg CO_2e)
Jeswani et al. 2019[4]	26.3	0.54
Wilkinson et al. 2019[19]	28	1
Janson et al. 2019[20]	28	0.60
Panigone et al. 2021[21]	16.4 – 23.8	0.96
Pernigotti et al. 2021[22]	14.28	0.6

^specifically SABA, if study broke down results by different pMDIs

Most studies not only compared the GWP of different inhalers, but analyzed scenarios of different interventions for the impact to their country in terms of both spending and CO_2e emissions.
Jeswani et al. found that replacing all pMDIs with DPIs would achieve high reductions in GWP and ozone depletion (96% and 94%) but this would happen at the expense of other impacts including marine eutrophication, photochemical oxidants formation, and fossil depletion, which would be 2-6 times higher than current.[4]

Wilkinson et al. found that, in England, switching from MDIs to DPI could either increase or decease costs, depending which DPIs were used.[19] For every 10% of MDIs changed to DPIs, 58 kt CO_2e could be saved, and £8.2M could be saved if the cheapest equivalent DPI is used.

A study by Janson et al. compared inhaler prescribing in England to Sweden.[20] For SABAs, 94% of use in England was in the form of pMDIs compared to 10% in Sweden. If England had the same rates of pMDI use as Sweden, 550 kt CO_2e would be saved annually.

Limitations

- Some pharmaceutical companies are using life-cycle assessment of their products to identify their environmental impacts however, such assessments are not often available in the public domain.

- Inhaler products, manufacturing processes, and amounts of non-medicinal ingredients may differ between countries. There is no available research on this question that has been conducted in Canada. None of the included studies assessed a terbutaline DPI.
- Two of the included studies[21,22] were sponsored by industry, and it should be noted that some companies may gain a commercial advantage from a switch to DPIs.

Question 2 (clinical outcomes):

a) Search Strategy - *See Appendix 3. Search Strategy*

- **Data sources:** Canadian Agency for Drugs & Technologies in Health (CADTH), Cochrane Database of Systematic Reviews, CENTRAL, MEDLINE, Embase. Search was conducted Mar 4, 2022.
- **Search terms:** salbutamol, albuterol, terbutaline, asthma, chronic obstructive pulmonary disease, randomized controlled trial

b) Publication restrictions: English, 1987 to current (1987 was Montreal Protocol banning CFCs in pMDI)

c) Study selection criteria:

- Design: Randomized controlled trials
- Population: Adult patient with COPD or asthma
- Intervention/Comparison: salbutamol inhaled vs. terbutaline inhaled
- Outcomes: Efficacy (spirometry: PEF or FEV1, symptom scores, need for additional doses, patient preference) and safety (tachycardia, tremor, study withdrawal due to adverse effects)

d) Trial Flow Diagram - *See Appendix 4. Trial Flow Diagram*

e) Trial summaries

Only three small studies conducted between 1994-2000 met the inclusion criteria for the literature review.[23–25] See the trial overview and results table below. One study found that terbutaline via Turbuhaler (DPI) improved mean peak expiratory flow (PEF) compared to salbutamol via Rotahaler (DPI). No other statistically significant differences were found in other outcome measures, or in the other two studies.

*DISCLAIMER – The data regarding numbers of inhalers used and their cost provincially and at Island Health are confidential and have been edited with fictional numbers to illustrate an example analysis.

Table 4. Summary of studies comparing inhaled terbutaline and salbutamol

Trial	Design	Population	Intervention/Comparator	Primary	Secondary
Lindsay et al. 1994[23]	Randomized, open-label, cross-over	27 adults and 20 children (7 years or older) with moderate asthma (already using a salbutamol pMDI BID), no recent severe exacerbations	terbutaline 0.5 mg via Turbuhaler (DPI) vs. salbutamol 0.2 mg via pMDI, both given BID + q4h prn, over 4 week treatment period each	*PEF % predicted (pre-β2-agonist):* 79% vs. 79% (p = 0.6) *PEF % predicted (post-β2-agonist):* 89% vs. 90% (p = 0.1)	*FEV_1:* 71 vs. 72 (p = 0.3) *FVC*: 84 vs. 85 (p = 0.3) *Total symptom score:* 1.8 vs. 2.0 (p = 0.3) *Patient preference:* 44% terbutaline, 39%, salbutamol, 17% no preference No difference in adverse events
Gioulekas et al. 1996[24]	Randomized, open-label, cross-over	32 adults with asthma who were taking regular β2 agonist therapy	terbutaline Turbuhaler (DPI) 0.5 mg TID + prn vs. salbutamol Rotahaler (DPI) 0.4 mg TID + prn each given for 3 weeks	*Mean morning PEF:* 4261 min^{-1} vs. 4101 min^{-1} (p=0.016) *Mean evening PEF*: 4461 min^{-1} vs. 4281 min^{-1} (p=0.008)	No statistically significant differences in diary symptoms scores, use of additional study drug, patient preference, or serious adverse events
Malinen et al. 2000[25]	Randomized, cross-cover, double-blind, double-dummy	29 adult patients with stable asthma without previous experience with the tested devices	Single doses of salbutamol 0.1 mg via Easyhaler (DPI) vs. terbutaline 0.25 mg via Turbuhaler (DPI)	*FEV_{1max}*: 3.14 L vs 3.07 L (95% CI -0.01 to 0.20 L)	No statistically significant differences in: max % change in FEV_1, AUC of FEV_1, patient preference

Limitations

- Two trials were open-label.[23,24]
- All three trials conducted *a priori* sample size calculations. However, two studies lost patients to follow up or to protocol violations and used "all patients treated" statistical analysis. [23,24] Therefore, these two trials may not have been powered to detect a difference in their primary outcomes.
- The results of these studies may have limited external validity in 2022. In the last 25 years, recommendations for the management of asthma have changed. For example, in Lindsay et al. 17% and 20% of patients in each group were using concomitant theophylline[23], a drug which is used much less commonly today. In addition, two studies[24,25] compared terbutaline via Turbuhaler to salbutamol via a different DPI (Rotahaler and Easyhaler) – devices that are not currently marketed in Canada.
- No funding sources or conflicts of interest were declared. Two studies had co-authors who were employed by the pharmaceutical industry.[23,25]

6. ECONOMIC REVIEW

In some countries DPIs are widely prescribed for the treatment of asthma and COPD (90% of SABA use in Sweden is via DPI).[20] However, younger children and some patients with severe asthma or severe COPD (particularly the elderly) may not always be able to generate an adequate inspiratory flow to ensure optimal medication delivery from all DPIs. Therefore, there will always be some patients who require salbutamol pMDIs. Cost to health authorities will largely depend on if there is a cultural shift in prescribing patterns towards the use of DPIs in BC.

*DISCLAIMER – The data regarding numbers of inhalers used and their cost provincially and at Island Health are confidential and have been edited with fictional numbers to illustrate an example analysis.

Last year in BC Health Authorities, 0.13%* of all SABA inhaler purchases were for terbutaline. Therefore a 10-fold increase (1.3%) was arbitrarily used as the switch rate for the low end of the budget impact analysis. Fifty percent was chosen as the high-end for the switch rate, based on the NHS target (England, similar to BC, uses >90% pMDIs for SABA inhalers).

As the average patient admitted to hospital is not admitted long enough to require more than one inhaler, the budget impact analysis compared the costs of whole inhalers, rather than the price per dose of medication.

Table 5. Acquisition cost of terbutaline and its comparators

Product	Actuations per inhaler	Cost per Inhaler
salbutamol 100 mcg/puff pMDI *Ventolin HFA, generics*	200	$6.50*
salbutamol 200 mcg/puff DPI *Ventolin Diskus*	60	$10.72*
terbutaline 500 mcg/puff DPI *Bricanyl Turbuhaler*	120	$10.19*

Table 6. BC Health Authorities Purchasing Data (Apr 1, 2020 to Mar 31, 2021)

	Number of inhalers				
	LMPS	VIHA	NH	IH	**Total**
salbutamol 100 mcg/puff pMDI *Ventolin HFA, generics*	XXX	25,000*	XXX	XXX	**100,000***
salbutamol 200 mcg/puff DPI *Ventolin Diskus*	X	X	X	X	**30***
terbutaline 500 mcg/puff DPI *Bricanyl Turbuhaler*	X	X	X	X	**120***

Table 7. BC Health Authorities Budget Impact Analysis*

Products	Cost in FY 2020-21	New cost if 1.3% switch to terbutaline	New cost if 50% switch to terbutaline
salbutamol 100 mcg/puff pMDI *Ventolin HFA, generics*	$650,000*	$641,550*	$325,000*
terbutaline 500 mcg/puff DPI *Bricanyl Turbuhaler*	$1,222.80*	$14,469.80*	$510,722.80*
Total Annual Cost (all health authorities)	**$651,222.80* (cost in 2020-21)**	**$656,019.80* (an increase of $4,797* per year)**	**$835,722.80* (an increase of $184,500* per year)**

*DISCLAIMER – The data regarding numbers of inhalers used and their cost provincially and at Island Health are confidential and have been edited with fictional numbers to illustrate an example analysis.

7. ENVIRONMENTAL REVIEW

To conduct an environmental impact analysis for BC hospitals, the average kg CO_2e per inhaler from the five studies included in the literature review was calculated. For pMDI the mean kg CO_2e was 25.0 (range 14.3 – 28.3) and for DPI the mean kg CO_2e was 0.7 (range 0.5 – 1.0). Using the same purchasing data and low and high switch rates as the budget impact analysis*(Table 7), the carbon footprints were calculated.

Table 8. BC Health Authorities Environmental Impact Analysis*

Products	**tCO_2e in FY 2020-21**	**New tCO_2e if 1.3% switch to terbutaline**	**New tCO_2e if 50% switch to terbutaline**
salbutamol 100 mcg/puff pMDI *Ventolin HFA, generics*	2,500*	2,467*	1,250*
terbutaline 500 mcg/puff DPI *Bricanyl Turbuhaler*	0.1*	1*	35*
Total Annual Cost (all health authorities)	**2,500* (tCO_2e in 2020-21)**	**2468* (a decrease of 32* tCO_2e per year)**	**1285*(an decrease of 1215* tCO_2e per year)**

If 50% of the salbutamol pMDIs purchased by BC Health Authorities were replaced by terbutaline DPIs, this would result in 1285* tonnes of CO_2e greenhouse gas emissions mitigated at a cost to the drug budget of $184,500*. This represents a cost of $144 per tonne CO_2e avoided*.

To put this into context, since 2014 Island Health has been accessing funding from the Province's Carbon Neutral Capital Program (CNCP) to implement greenhouse gas emissions reduction projects such as boiler upgrades, zone control, and heat recovery systems.[26] The average cost of reducing emissions through these projects has been $3,375/$tCO_2e$. Reducing greenhouse gas emissions through switching inhalers comes at a fraction (4.3%*) of the cost of what the health authorities spend on capital projects.

To put the climate change impact in perspective a few other ways:

- The greenhouse gas emissions from the salbutamol pMDIs purchased by Island Health is similar* to all the emissions of all Island Health fleet vehicles, and is more than that of all the paper used by the health authority (see Table 9).
- If 50% of the salbutamol pMDIs purchased by BC Health Authorities were switched to terbutaline DPIs, the reduction in our carbon footprint annually would be the same as 996* people going vegetarian (based on an average impact of 1.29 tCO_2e/capita/year[27]) or 264* typical passenger vehicles being taken off the road (based on an average 4.6 tCO_2e/vehicle/year[28]).

Table 9. Comparing the carbon footprint of salbutamol pMDI to other sectors in Island Health

Island Health 2020[26]			**Island Health FY 2020-21**
Fleet [tCO2e]	**Office Paper [tCO2e]**	**Buildings [tCO2e]**	**salbutamol pMDI [tCO2e]**
644	547	29092	625*

8. SAFETY REVIEW

- See Appendix 6. Formulary Addition Safety Guidance List

There are no specific safety concerns with terbutaline inhaler.

*DISCLAIMER – The data regarding numbers of inhalers used and their cost provincially and at Island Health are confidential and have been edited with fictional numbers to illustrate an example analysis.

9. DISCUSSION

Interpretation of results:

1. Can the results be applied to our patients?
The available environmental evidence has consistently shown that pMDIs contribute far more to greenhouse gas emissions compared to DPIs, due to their HFC propellants. However, most of the source data is not available in the public domain and comes from industry who may have a financial incentive to move toward DPI use. DPIs also performed worse on other outcomes such as marine eutrophication, photochemical oxidants formation, and fossil depletion. In addition, manufacturing processes and materials may be different between countries and between different products in a class. None of the environmental impact studies were conducted in Canada or studied terbutaline (BRICANYL TURBUHALER).

Very limited clinical evidence exists directly comparing inhaled terbutaline to inhaled salbutamol for the treatment of asthma or COPD in adults. The available evidence is over 20 years old and may have limited generalizability to our current population due to changes in asthma management over time.

2. Were all-important outcomes considered?
The environmental studies included in this literature review used the outcome of climate change impact, measured in kg CO_2e, which is considered the most important environmental impact factor.

The lung function measurements (e.g. FEV_1 and PEF) used in the included trials are accepted endpoints in asthma studies.[29] Other clinically important outcomes, such as hospitalization or mortality, were not measured. However, these outcomes may not be feasible to study due to large sample size requirements.

3. Are the benefits worth the harm & cost?
The limited available evidence suggests that terbutaline is an effective short-acting beta-agonist when used to relieve asthma symptoms. No study or outcome measure found terbutaline to be less effective or safe compared to salbutamol. One study found that terbutaline improved PEF compared to salbutamol.

4. Construct a "balance sheet"
With presumably similar efficacy and safety, terbutaline contributes less greenhouse gas emissions (estimated ↓ 24 kg CO_2e/inhaler) but comes at an increased cost (↑ $3.69*/inhaler) compared to salbutamol pMDI.

Compared to salbutamol DPI (VENTOLIN DISKUS), terbutaline has presumably similar efficacy and safety, and similar greenhouse gas emissions, but comes at a lower cost (↓ $0.53*/inhaler).

If prescribing practice does not significantly change from current community patterns, adding terbutaline to formulary will have a negligible budgetary or carbon footprint impact. However, if prescribing culture moves toward more DPI use, it is estimated up to 50% of salbutamol pMDI use could be replaced by terbutaline DPI at an increased cost to health authorities of $184,500* per year. This 50% switch rate would mitigate an estimated 1215* tonnes of CO_2e emissions per year.

*DISCLAIMER – The data regarding numbers of inhalers used and their cost provincially and at Island Health are confidential and have been edited with fictional numbers to illustrate an example analysis.

10. SUMMARY

Internal Health Authority Concerns

Terbutaline DPI (BRICANYL TURBUHALER) would be the best choice of a SABA DPI for BCHAs to carry as it is also a benefit with BC PharmaCare, allowing for continuity of care, and a less expensive option than salbutamol DPI (VENTOLIN DISKUS) which is not a PharmaCare benefit. It may be preferred by hospitals to carry only one SABA DPI to save on shelf space. We do not anticipate that removing salbutamol DPI (VENTOLIN DISKUS) will cause significant disruption, as it is a low usage item (X inhalers in the last year across all HAs).

A.	Should this drug be added to Formulary? [Specify: Formulary, Formulary-Restricted (include restrictions) or Excluded]	Formulary
B.	What is the budget impact should this be added to the Formulary?	An estimated increased cost of $4,797* to $184,500* depending on uptake
C.	If added, is there risk in inappropriate use of this agent and if so, outline any concerns.	No
D.	If added, should any existing formulary agent be deleted from the Formulary?	Yes, salbutamol DPI (VENTOLIN DISKUS) should be removed due to low usage and to align with PharmaCare coverage
E.	If added, are there any particular implementation issues which need to be addressed (e.g., staff education, staff communication)?	Staff education on new inhaler device
F.	If added, does this medication need to be added to the provincial hazardous drug classification?	No
G.	If added, should utilization of this drug be monitored?	No

11. PROPOSAL

Date	Proposal	Comment
June 23, 2022	THAT terbutaline respiratory (inhaled) powder (BRICANYL TURBUHALER) be added to formulary without restrictions. THAT salbutamol respiratory (inhaled) powder (VENTOLIN DISKUS) be removed (excluded) from formulary.	

12. P&T DECISION

Date	Decision

13. REFERENCES

1. Health Canada Drug Product Database. BRICANYL TURBUHALER Product Monograph. AstraZeneca Canada Inc [Internet]. [cited 2021 Jan 26]. Available from: https://health-products.canada.ca/dpd-bdpp/
2. British Thoracic Society. Position Statement: The Environment and Lung Health 2020 [Internet]. 2020. Available from: https://www.brit-thoracic.org.uk/
3. Wilkinson AJK, Anderson G. Sustainability in Inhaled Drug Delivery. Pharm Med. 2020 Jun 4;34(3):191–9.
4. Jeswani HK, Azapagic A. Life cycle environmental impacts of inhalers. J Clean Prod. 2019 Nov;237:117733.
5. Centre for Sustainable Healthcare. Inhalers and NHS Long Term Plan | CSH Networks [Internet]. [cited 2022 Jan 28]. Available from: https://networks.sustainablehealthcare.org.uk/networks/sustainable-respiratory-care/inhalers-and-nhs-long-term-plan
6. United Nations Industrial Development Organization. The Montreal Protocol evolves to fight climate change [Internet]. [cited 2022 Jan 28]. Available from: https://www.unido.org/our-focus-safeguarding-environment-implementation-multilateral-environmental-agreements-montreal-protocol/montreal-protocol-evolves-fight-climate-change
7. Pritchard JN. The Climate is Changing for Metered-Dose Inhalers and Action is Needed. Drug Des Devel Ther. 2020 Jul;Volume 14:3043–55.
8. International Organization for Standardization. ISO 14067:2018 greenhouse gases — carbon footprint of products — requirements and guidelines for quantification. [Internet]. Available from: https://www.iso.org/standard/71206.html
9. R. Andrew McIvor. Chronic Obstructive Pulmonary Disease In: Compendium of Therapeutic Choices [Internet] [Internet]. Canadian Pharmacists Association; 2021 [cited 2022 Mar 16]. Available from: https://www.myrxtx.ca
10. Alan Kaplan. Asthma in Adults and Adolescents. In: Compendium of Therapeutic Choices [Internet] [Internet]. Canadian Pharmacists Association; 2021 [cited 2022 Mar 16]. Available from: https://www.myrxtx.ca
11. Gliklich RE, Castro M, Leavy MB, Press VG, Barochia A, Carroll CL, et al. Harmonized outcome measures for use in asthma patient registries and clinical practice. J Allergy Clin Immunol. 2019 Sep 1;144(3):671–681.e1.
12. Glaab T, Vogelmeier C, Buhl R. Outcome measures in chronic obstructive pulmonary disease (COPD): strengths and limitations. Respir Res. 2010 Jun 17;11(1):79.
13. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. [Internet]. Available from: www.ginasthma.org
14. Global Initiative for Chronic Obstructive Lung Disease. Global Stategy for the Diagnosis, Management, and Prevention of Chronic Obstrutcive Pulmonary Disease (2020 Report) [Internet]. Available from: https://goldcopd.org/gold-reports/
15. National Institute for Health and Care Excellence. Patient Decision Aid: Inhalers for asthma [Internet]. 2020 [cited 2022 Mar 16]. Available from: https://www.nice.org.uk/guidance/ng80/resources/inhalers-for-asthmapatient-decision-aid-pdf-6727144573
16. Liew K, Wilkinson A. How do we choose inhalers? patient and physician perspectives on environmental, financial and ease-of-use factors. In BMJ Publishing Group Ltd and British Thoracic Society; 2017 [cited 2022 Mar 16]. p. A235–A237. Available from: https://thorax.bmj.com/lookup/doi/10.1136/thoraxjnl-2017-210983.422
17. Huijbregts MAJ, Steinmann ZJN, Elshout, PMF, Stam G. ReCiPe 2016 v1.1 A harmonized life cycle impact assessment method at midpoint and endpoint level Report I: Characterization [Internet]. National Institute

for Public Health and the Environment, The Netherlands; 2017. Available from: https://pre-sustainability.com/legacy/download/Report_ReCiPe_2017.pdf

18. European Commission, Joint Research Centre, Cerutti A, Pant R, Sala S. Development of a weighting approach for the environmental footprint. Publications Office; 2018.

19. Wilkinson AJK, Braggins R, Steinbach I, Smith J. Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. BMJ Open. 2019 Oct 29;9(10):e028763.

20. Janson C, Henderson R, Löfdahl M, Hedberg M, Sharma R, Wilkinson AJK. Carbon footprint impact of the choice of inhalers for asthma and COPD. Thorax. 2020 Jan;75(1):82–4.

21. Panigone S, Sandri F, Ferri R, Volpato A, Nudo E, Nicolini G. Environmental impact of inhalers for respiratory diseases: decreasing the carbon footprint while preserving patient-tailored treatment. BMJ Open Respir Res. 2020 Mar 31;7(1):e000571.

22. Pernigotti D, Stonham C, Panigone S, Sandri F, Ferri R, Unal Y, et al. Reducing carbon footprint of inhalers: analysis of climate and clinical implications of different scenarios in five European countries. BMJ Open Respir Res. 2021 Dec 6;8(1):e001071.

23. Lindsay DA, Russell NL, Thompson JE, Warnock TH, Shellshear ID, Buchanan PR. A multicentre comparison of the efficacy of terbutaline Turbuhaler™ and salbutamol perssurized metered dose inhaler in hot, humid regions. Eur Respir J. 1994 Feb 1;7(2):342–5.

24. Gioulekas D, Papakosta D, Vordoyianni P, Baloti H, Vamvalis C. A comparison of the clinical efficacy and patient acceptability of terbutaline Turbuhaler and salbutamol Rotahaler, in adult patients with asthma. Respir Med. 1996 Apr;90(4):205–9.

25. Malinen A, Hedman J, Koskela T, Silvasti M, Toivanen P. Salbutamol via Easyhaler Produces Equivalent Bronchodilation to Terbutaline via Turbuhaler following Inhalation of a Single Dose of Equipotent Beta 2-Sympathomimetic: Clin Drug Investig. 2000 Sep;20(3):165–71.

26. Green Island Health. 2020 Climate Change Accountability Report [Internet]. Available from: https://intranet.islandhealth.ca/green/Documents/reports/island-health-ccar-2020.pdf

27. Canadians are among the world's worst carbon emitters. Here's what we can do about it | CBC News [Internet]. [cited 2022 Mar 15]. Available from: https://www.cbc.ca/news/science/how-canadians-can-cut-carbon-footprints-1.6202194

28. Greenhouse Gas Emissions from a Typical Passenger Vehicle | US EPA [Internet]. [cited 2022 Mar 15]. Available from: https://www.epa.gov/greenvehicles/greenhouse-gas-emissions-typical-passenger-vehicle

29. Halpin DMG, Meltzer EO, Pisternick-Ruf W, Moroni-Zentgraf P, Engel M, Zaremba-Pechmann L, et al. Peak expiratory flow as an endpoint for clinical trials in asthma: a comparison with FEV1. Respir Res [Internet]. 2019 Jul 18;20(1). Available from: https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-019-1119-6

30. ISMP warns of critical issue with drug mix-up | 2004-06-01 | AHC Media: Continuing Medical Education Publishing | Relias Media - Continuing Medical Education Publishing [Internet]. [cited 2022 Mar 15]. Available from: https://www.reliasmedia.com/articles/4987-ismp-warns-of-critical-issue-with-drug-mix-up

31. NIOSH List of Antineoplastic & Other Hazardous Drugs in Healthcare Settings, 2016 | NIOSH | CDC [Internet]. [cited 2022 Mar 15]. Available from: https://www.cdc.gov/niosh/docs/2016-161/default.html

14. APPENDICES

Appendix 1. Hierarchy of Outcomes

Clinical outcome	Comments
All-cause mortality	- Almost always the highest rank
Non-fatal serious adverse events (AE's)	- See definitions below
Quality of life (QOL)	- Using validated general or disease-specific QOL instruments
Withdrawal due to adverse events	- See definitions below
Clinical outcomes or efficacy scales	- Using valid, reliable scales with a defined minimum clinically important difference (MCID) detectable in the clinical care of patients
Health resource utilization	- May include ED visits, hospitalization, need for medical procedures, etc.
Total AE's/ADR's	- See definitions below
Surrogate markers	- Using markers previously shown to be associated with improvements in clinically-important outcomes

This table is intended to be an example only, and the specific hierarchy may change based on evidence or previously revealed patient or clinician preferences for clinical outcomes in a certain disease states.

Definitions

1. Adverse event (definition)
"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment". An adverse event can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medical product.

2. Serious adverse event (definition)
- "Any untoward medical occurrence that at any dose; results in death, if life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity , or is a congenital abnormality/birth defect".

3. Adverse drug reaction (definition)
- The definition differs slightly depending on the status of the drug product (i.e. pre-approval versus marketed products)

a) Pre-approval: *"All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions".*

b) Post-marketing: *"A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, of therapy of a disease or for modification of physiological function".*

Appendix 2. Hierarchy of Evidence

Level	Trial Design
1a	Systematic review or meta analysis (of randomized, controlled trials)
1b	Randomized, controlled trial (RCT)
2a	Non-randomized, controlled trial
2b	Quasi-experimental trials (quasi-randomized, controlled before-after (CBA trial), interrupted time series trials (ITS))
3	Observational trials (cohort, case-control, and cross-sectional)
4	Expert opinions or pathophysiologic rationale

Adapted from the Centre for Evidence-Based Medicine (CEBM):
http://www.cebm.net/index.aspx?o=1025

Appendix 3. Search Strategy

Question 1: Environmental Outcomes

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 27, 2022>

1	Administration, Inhalation/	32804
2	Adrenergic beta-Agonists/ad [Administration & Dosage]	3127
3	Asthma/dt [Drug Therapy]	38057
4	"Nebulizers and Vaporizers"/	9870
5	Pulmonary Disease, Chronic Obstructive/dt [Drug Therapy]	9020
6	Carbon Footprint/	802
7	Greenhouse Effect/	5919
8	Greenhouse Gases/	1398
9	Global Warming/	3871
10	1 or 2 or 3 or 4 or 5	74341
11	6 or 7 or 8 or 9	11027
12	10 and 11	22

Embase <1974 to 2022 January 27>

1	inhalational drug administration/	48934
2	beta adrenergic receptor stimulating agent/	22603
3	asthma/dt [Drug Therapy]	55286
4	chronic obstructive lung disease/dt [Drug Therapy]	21145
5	nebulizer/	9292
6	vaporizer/	1012
7	carbon footprint/	9880
8	greenhouse effect/ or greenhouse gas/	20979
9	global warming.mp.	10902
10	1 or 2 or 3 or 4 or 5 or 6	134355
11	7 or 8 or 9	32837
12	10 and 11	51

EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 26, 2022>

1	administration, inhalation.mp. [mp=title, short title, abstract, full text, keywords, caption text]	120
2	adrenergic beta-agonists.mp. [mp=title, short title, abstract, full text, keywords, caption text]	57
3	asthma.mp. [mp=title, short title, abstract, full text, keywords, caption text]	841
4	chronic obstructive pulmonary disease.mp. [mp=title, short title, abstract, full text, keywords, caption text]	466
5	vaporizers.mp. [mp=title, short title, abstract, full text, keywords, caption text]	38
6	carbon footprint.mp. [mp=title, short title, abstract, full text, keywords, caption text]	0
7	greenhouse effect.mp. [mp=title, short title, abstract, full text, keywords, caption text]	0
8	greenhouse gases.mp. [mp=title, short title, abstract, full text, keywords, caption text]	1
9	global warming.mp. [mp=title, short title, abstract, full text, keywords, caption text]	3
10	1 or 2 or 3 or 4 or 5	1105
11	6 or 7 or 8 or 9	4
12	10 and 11	2

CADTH Search
Search term: terbutaline
No results

Question 2: Clinical Outcomes

Embase <1974 to 2022 March 03>

1	*salbutamol/	12184
2	*terbutaline/	5353
3	asthma/	248166
4	chronic obstructive lung disease/	152878
5	*randomized controlled trial/	11451
6	3 or 4	375014
7	1 and 2	1880
8	5 and 6 and 7	0
9	limit 8 to (human and yr="1987-Current")	0

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to March 03, 2022>

1	*Albuterol/	6226
2	*Terbutaline/	1922
3	Asthma/	133382
4	Pulmonary Disease, Chronic Obstructive/	45915
5	Randomized Controlled Trial/	560038
6	1 and 2	142
7	3 or 4	174372
8	5 and 6 and 7	35
9	limit 8 to (english language and humans and yr="1987 -Current")	25

EBM Reviews - Cochrane Central Register of Controlled Trials <January 2022>
EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 2, 2022>

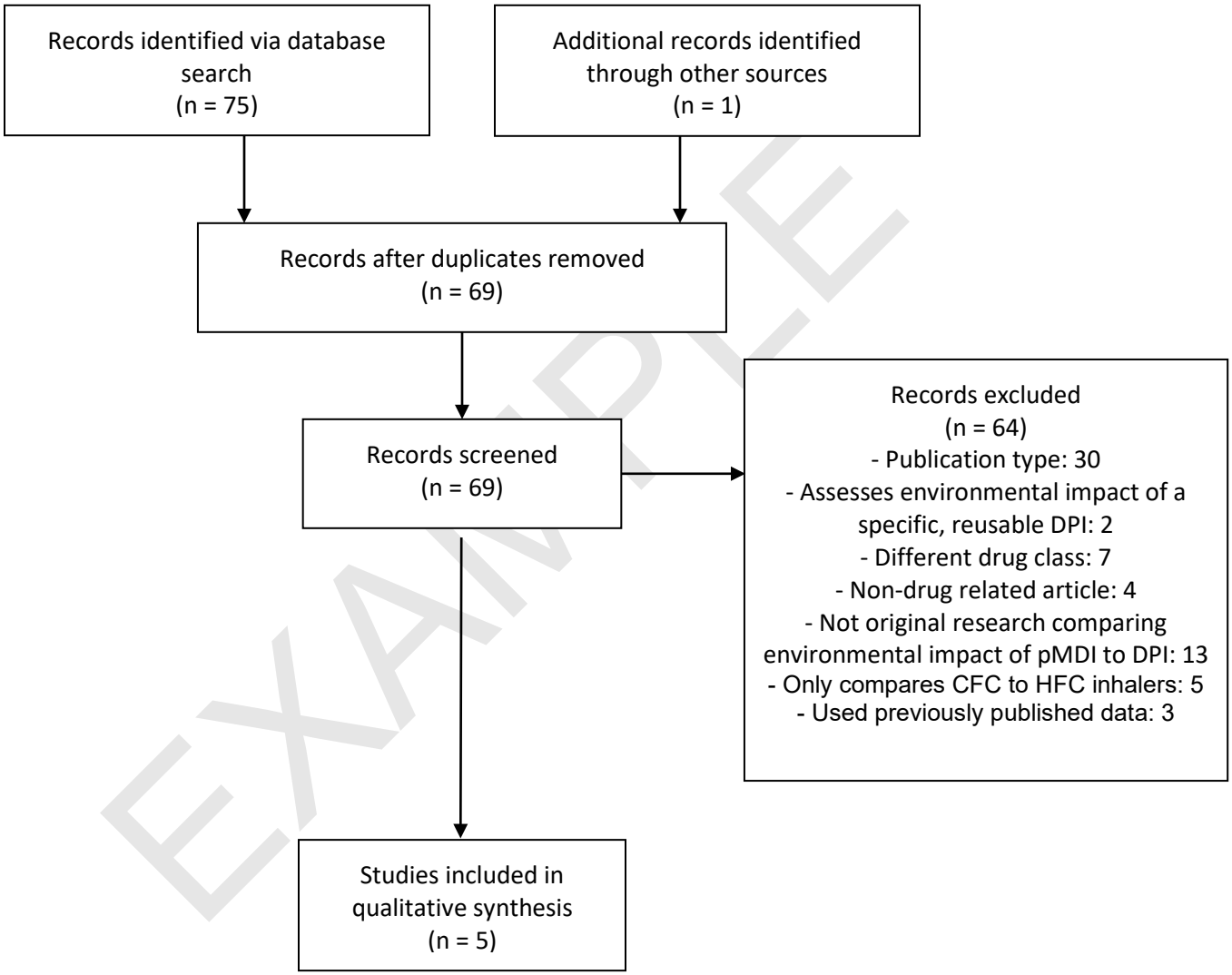
1	salbutamol.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	5043
2	albuterol.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	4187
3	1 or 2	7150
4	terbutaline.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	1583
5	asthma.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	35012
6	Pulmonary Disease, Chronic Obstructive.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	6086
7	Randomized Controlled Trial.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	608519
8	3 and 4	312
9	5 or 6	40677
10	7 and 8 and 9	60
11	limit 10 to english language	52
12	limit 11 to yr="1987 -Current"	52

CADTH Search
Search term: terbutaline
No results

Appendix 4. **Trial Flow Diagram**

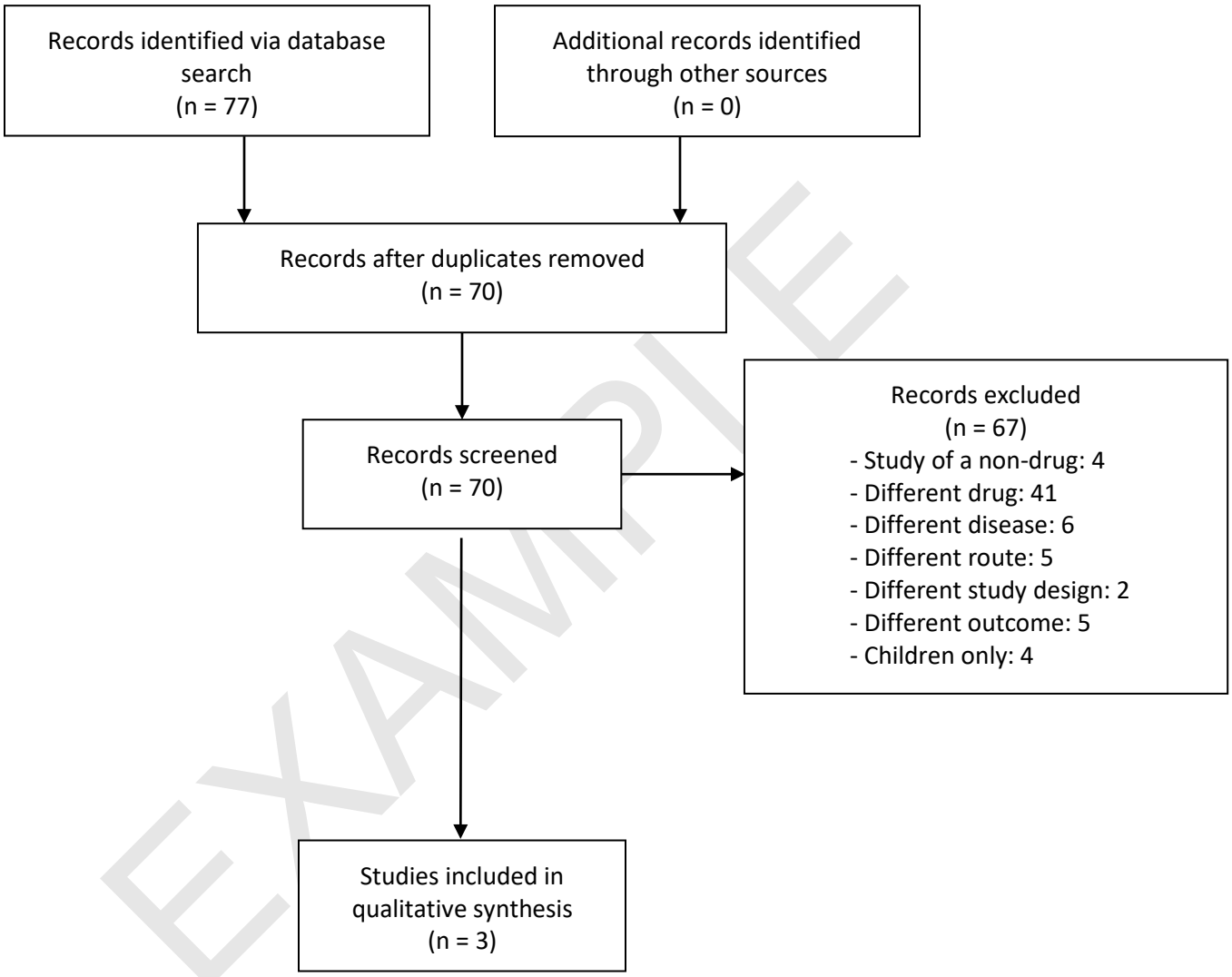
Study Flow Diagram

Question 1. Environmental Outcomes



Study Flow Diagram

Question 2. Clinical Outcomes



<u>Appendix 5.</u> Trial Overview & Results Tables

Jeswani et al. 2019[4]

Countries	England	
Intervention/ Comparator	pMDI (using HFC-134a, HFC-227ea, or HFC-152a propellant) and DPI	
Methods	Environmental impacts estimated through LCA (life cycle assessment) using ISO 14040/14044 guidelines (standards for assessing carbon footprint) from cradle to grave including production of the device and propellants, the use, and end-of-life disposal. The first analysis is carried out for the individual inhalers, with the functional unit defined as "delivery of 1 dose of inhaled medicine". The second analysis considers impacts based on the annual usage of inhalers in the UK.	
Data Sources	Data obtained directly from industry, supplemented by literature, and Ecoinvent database	
Results	**Global warming potential (GWP):** HFC-227ea pMDI: 697 g CO_2e/dose HFC-134a pMDI: 263 gCO_2e/dose HFC-152a pMDI: 20 CO_2e/dose DPI: 9 g CO_2e/dose	**Analysis based on UK inhaler usage:** Replacing all pMDIs with DPIs would achieve high reductions (94-96%) for GWP and ozone depletion. However, this would happen at the expense of several other impacts which would increase significantly. The most notable increases would be for marine eutrophication, photochemical oxidants formation, and fossil depletion, which would be 2-6 times higher than current.

Wilkinson et al. 2019[19]

Countries	England
Intervention/ Comparator	High global warming potential (GWP) inhalers versus low GWP inhalers
Methods	Inhalers were categorized by mechanism of action (e.g. short acting beta-agonist). Within each category, the cost and carbon impact of changing from a low GWP to high GWP inhaler was calculated.
Data Sources	- National Health Service prescription data from England in 2017 - Reviewed available data on the carbon footprint of inhalers from scientific publications, independently certified reports and patents
Results	**GWP:** For every 10% of MDIs changed to DPIs, 58 kt CO2e could be saved annually in England. **Costs:** If MDIs using HFC propellant are replaced with the cheapest equivalent DPI, then for every 10% of MDIs changed to DPIs, drug costs decrease by £8.2M annually. However if the brands of DPIs stay the same as 2017 prescribing patterns, for every 10% of MDIs changed to DPIs, drug costs increase by £12.7M annually. **SABA specific analysis:** • Salbutamol MDI to salbutamol DPI "Easyhaler" (UK product) • Current spending on salbutamol MDI: £58.2M • Cost increase for every 10% switch : £3.1M • GWP: Ventolin pMDI 28 kg CO_2e/inhaler versus DPI: 1 kg CO_2e/inhaler

Janson et al. 2019[20]

Countries	England, Sweden	
Intervention/ Comparator	Three ICS and long-acting β2-agonist combinations Relvar Ellipta (fluticasone furorate/vilanterol) (DPI), Seretide Accuhaler (fluticasone propionate/salmeterol) (DPI), Seretide Evohaler (MDI) and two short acting β2-agonists Ventolin Accuhaler (salbutamol) (MDI), and Ventolin Evohaler (MDI)	
Methods	- Compared environmental impact using calculated carbon footprint data - Compared the inhaler-related carbon footprint impact between England and Sweden and the potential for reduction of annual carbon footprint in England if the pattern of devices chosen resembled that of Sweden	
Data Sources	- GlaxoSmithKline life cycle analysis data - Prescription data from England and Sweden in 2017	
Results	**Carbon footprint in kg CO_2e/inhaler**: Ventolin Evohaler (MDI) = 28 Seretide Evohaler (MDI) = 19 Ventolin Accuhaler (DPI) = 0.60 Seretide Accuhaler (DPI) = 0.90 Relvar Ellipta (DPI) = 0.80	**England vs Sweden MDI rates:** Overall MDI rate: 70% vs 13% SABA MDI rate: 94% vs 10% If England had the same rates of MDI use as Sweden, 550 kt CO2e would be saved annually

Panigone et al. 2021[21]

Countries	Italy
Intervention/ Comparator	Clenil (beclometasone dipropionate) MDI, Foster (extrafine beclometasone/ formoterol) MDI and Foster NEXThaler DPI, Trimbow (extrafine beclometasone/formoterol/glycopyrronium) MDI
Methods	Quantified the carbon footprint of specific products using whole product lifecycle analysis based on ISO 14067-2018 standard and guideline
Data Sources	Pharmaceutical company *Chiesi Farmaceutici SpA* (Italy) and certified through a third party
Results	**Carbon footprint in g CO_2e/actuation**: MDI products: 82 -119 DPI: 8

Pernigotti et al. 2021[22]

Countries	UK, Italy, France, Germany and Spain
Intervention/ Comparator	pMDIs versus DPI/SMIs
Methods	Evaluated four possible scenarios: (1) Imposing a switch from pMDIs to DPI/SMIs; (2) Replacing current propellants used in pMDIs with a low-GWP propellant; (3) Clinical optimisation of asthma maintenance therapy to reduce SABA inhaler use; and (4) Inhaler end-of-life recycling. The 'current case' (2019 emissions data) served as the framework against which emission reductions over a 10-year period from 2020 to 2030 were estimated.
Data Sources	Data used in this study were internally verified and provided by the sponsor (*Chiesi Farmaceutici*, Italy) or were retrieved from peer-reviewed publications or recognised databases by Aequilibria (Venezia, Italy)
Results	Carbon footprint per month of treatment (kg CO_2e): pMDI: 7.5 to 36.5 (salbutamol pMDI: 14.28 per canister) DPI: 0.6 to 1.25 SMI: 0.78 Impact on annual CO_2e emissions by scenario: (1) Switch from pMDIs to DPI/SMIs: 64-71% reduction (2) Switch to low-GWP pMDIs: 68-84% reduction (3) Minimizing SABA use: 17-48% (4) High rates of end-of-life recycling: 81-87%

Appendix 6. Formulary Addition Safety Guidance List

Consideration
Potential for Error - Terbutaline may have look-alike/sound-alike issues with methergine, terbinafine, and tolbutamide. - There has been an ISMP warning of confusing Methergine (methylergonavine parenteral injection) and Brethine (terbutaline parenteral injection).[30] However, this was with the parenteral rather than inhaled form of terbutaline. And, methylergonavine is not marketed in Canada.
Handling Precautions or Requirements BRICANYL TURBUHALER contains terbutaline sulfate which is sensitive to moisture. BRICANYL TURBUHALER should be stored with the cover tightened, at room temperature (15 - 30°C).[1] Terbutaline is not listed on the NIOSH List of Antineoplastic and Other Hazardous Drugs.[31]
"High Alert" Drug This is not a high-alert drug.
Parenteral Drug Requirements N/A
Other Considerations N/A