Curr Rheumatol Rep (2015) 17: 514
DOI 10.1007/s11926-015-0514-3

HEALTH ECONOMICS AND QUALITY OF LIFE (M HARRISON, SECTION EDITOR)

How Important Is Mode of Administration in Treatments for Rheumatic Diseases and Related Conditions?

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Published online: 23 April 2015

Abstract Many new drugs do not offer clinical benefits over existing treatments but provide potentially more convenient modes of administration. These include how frequently a treatment is given, how it is delivered, who gives the treatment, and whether there are any associated local adverse reactions. We reviewed studies in rheumatology that ask patients and society the value they assign to these aspects of treatment in comparison to the benefits and side effects and costs. We find that mode of administration is generally valued by both patients and society, but the extent depends on the context of the disease and the study participants. Respondents with a more severe disease seem to assign less value to mode and frequency of administration, and prioritize improvement in pain and function. However, patients with chronic, but less severe, disease seem to place greater value on mode of administration. Furthermore, respondents with experience of the treatments perceived to be more inconvenient assigned lower value to more convenient treatments. Unfortunately, we found few examples of studies that reported values in a format that could easily be incorporated into resource allocation decisions by payers.

Topical Collection on *Health Economics and Quality of Life*

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Keywords Economics · Quality of life · Mode of administration

Introduction

Increasingly, new drugs to market are minor variations of existing drugs, which act by a related mechanism of action and rarely provide clinical benefit over existing treatments [1]. It is estimated that the majority in the growth of drug budgets has gone on to such "me too" drugs [2]. While it is argued that these drugs do not provide "benefits" to patients [2], this assumes a narrow view where benefits are solely related to clinical improvements, thereby ignoring other process-related factors such the way drugs are administered.

Many newer drugs are delivered in a more convenient manner, either by providing a more desirable route of administration (for example, taken orally instead of injected) or by reducing the frequency of administration. For example, traditional disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis (RA) required weekly or biweekly intravenous infusions, whereas new-generation DMARDs provide similar clinical benefits [3] but require less frequent injections or can be taken orally. A recent review on the comparative effectiveness of these new-generation DMARDs concluded that the treatment a patient use should be driven by consideration of their "preferences regarding route of administration, frequency and perception of adverse effects, and out-of-pocket costs" [4].

Commentators have questioned whether payers should reimburse new drugs that do not offer any additional clinical benefit [2]. While there is anecdotal evidence that more convenient administration is a benefit of treatment valued by patients, providers, and payers, it is not well understood how this benefit compares to other aspects of treatment such as

effectiveness or side-effect profile. Further, given the high rates of non-adherence to many medications [5], convenience may have a spillover effect onto increasing utilization of treatment leading to better health and reduced costs [6, 7]. However, these aspects of new treatments are more difficult to quantify and require a causal hypothesis that begins by demonstrating that patients value the mode of administration.

In this paper, we review the rheumatology literature for evidence on how different aspects related to the mode of administration of treatment is valued. We seek to understand whether the value of mode of administration justifies the adoption of new drugs offering greater convenience. We also report on the challenges with this evidence and describe how this can be improved.

Measuring Values for Mode of Administration

Understanding how patients and other stakeholders value aspects of treatments has become recognized as an important area of research in health care and medicine. Consumer theory posits that the value we assign to a good or service is closely linked to our preferences for or against it. There are two approaches to measuring these preferences, and consequent values: revealed and stated. Revealed preferences are derived from observed consumer behavior where an individual's choice between different goods and services in a market place reveal what aspects they prefer and ultimately value. However, data on revealed preferences often does not exist, particularly in health care where a market, in the economic sense, is absent. As a consequence, research in health care has focused primarily on measuring stated preferences. These are derived from surveys and allow researchers to control the way in which preferences are elicited. Stated preference methods fall into two broad categories: methods that using ranking, rating, or choice designs to quantify preferences for various attributes of an intervention (often referred to as conjoint analysis or discrete choice experiments), or methods that directly elicit values (monetary or in terms of risk of death or length of life) relating to a treatment (including contingent valuation, willingness to pay, time trade off, and standard gamble). A distinction between these two categories is that the latter directly aims to derive preferences for certain characteristics (a time trade-off asks persons how much life they would be willing to sacrifice to live in full health), whereas the former aims to explore trade-offs between treatment attributes and its effect on choice.

Conjoint analysis has been widely used in marketing research [8, 9] and is becoming increasingly popular in health services research to explore a range of health-related services and treatments [10, 11]. Briefly, they work on the premise that any "product," for example, a healthcare treatment or drug therapy, can be described by levels of its characteristics, known as attributes. The extent to which an individual values the product is dependent on a weighted sum of the levels of these characteristics [12]. The results can determine whether, for example, patients prefer a hospital at close distance with fewer services to one that is farther away with a greater number of services or a product which provides greater benefit but has higher risks of side effects.

Discrete choice experiments (DCEs) are a form of conjoint analysis which is based on random utility theory (RUT) [13]. RUT states that the probability that product A is chosen over product B is proportional to how much product A is valued over product B. An example of a DCE is given in Fig. 1. Here, respondents are shown a series of hypothetical treatments with different levels depicted for each attribute and asked which they prefer. They will then be shown another choice where the levels for each treatment are changed. By asking a series of these types of questions, analysis can determine which levels are influencing choices, and by how much, indicating the strength of preference for each. Other forms of conjoint analysis exist, some combine a ranking task, and other using learning algorithms to pose choices that are more meaningful.

Two factors are important when interpreting conjoint studies. First, in most studies, the "value" derived is relative to the other attributes within the experiment. This can limit the ability to make comparisons with other studies that did not use the same attributes and/or levels. To overcome this limitation, attributes with general interpretation known as payment vehicles can be included, for example, cost or life-years, and used to estimate marginal rates of substitution (MRS) by dividing the coefficients for other attributes by the coefficient for this common denominator. These MRS can be interpreted as willingness to pay for the levels of an attribute (if a cost vehicle is used) or the health utility related to the levels of an attribute (if a life-years vehicle is used), compared to the reference level. Second, most DCEs do not enable the estimation of an individual's preferences, but rather the average of a sample of individuals. This can make it challenging to identify subgroups in the population that have significantly different preferences from each other. Other forms such as adaptive conjoint analysis do enable individual estimates, but studies still typically report the average of the entire sample.

Types of Modes of Administration Covered in Rheumatologic Studies

We synthesize evidence from 14 studies in rheumatology, which have sought to understand preferences for the way that drugs are administered. Studies have been conducted in a number of settings, most commonly in osteoporosis [14–20] and RA [21–25] and also in osteoarthritis (OA) [20, 26] and juvenile idiopathic arthritis (JIA) [27] (Table 1).

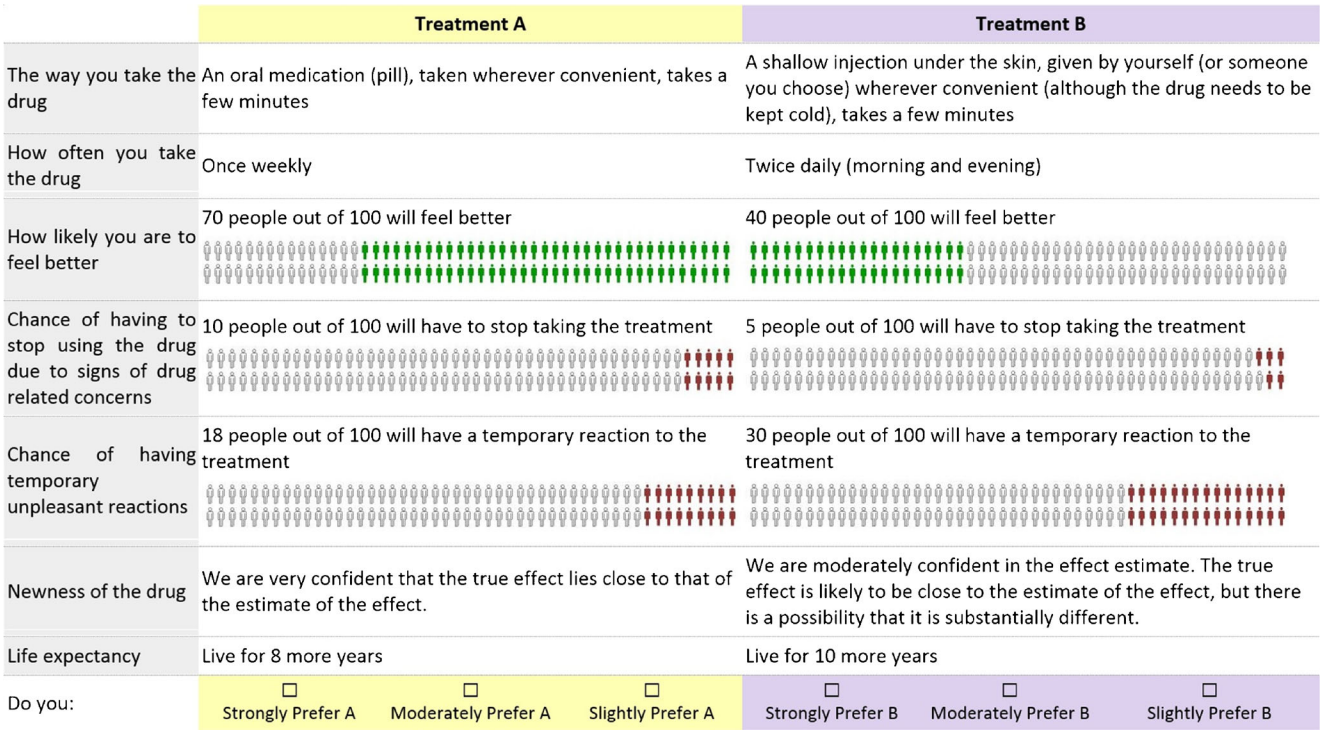

Fig. 1 Example DCE choice set from Harrison et al. [23]

The majority of studies looked to understand preferences from the patient perspective [14–22, 25, 26], but others have sought the preferences of parents (in the case of JIA), to compare patient and general practitioner preferences [15], or societal values [23]. Patient preferences have been sought to understand the decision-making process at the interface between patients and physicians, whereas the population sample was used to evaluate the value of health and non-health aspects of treatments from the societal perspective, which is meant to reflect the values used by decision makers when allocating health care resources. The study designs used to elicit preferences have consistently been DCE and conjoint analysis methodologies, which ask respondents to choose between alternative hypothetical treatments that reflect available treatment options.

Where patient preferences were sought, the majority of patient samples were experienced [14, 17, 20, 22, 25, 27] in the types of treatments or decision-making contexts which were presented to them in the experiments—e.g., they had been using medications with different modes of administration for some time. A smaller number of studies either selected patient samples naïve to the decision being presented [15, 21] or samples with a mixture of experience [16, 19, 26]. A single study looked at subgroups of respondents based on experience/naivety of treatment or their risk of negative outcomes at the time of the decision [19]. The study which elicited societal preferences in RA collected self-report information on the exposure to injectable treatments and experience of RA in a close family member or friend to understand their level of experience with either the disease or different types of treatment administration [23].

Preferences for a number of types of mode of administration have been described (Table 1). These include when a treatment is given (e.g., how often, for how long), where (e.g., in the home, at a physician's office or hospital), how (e.g., oral tablet or injection), who gives the treatment (e.g., yourself or a physician), and whether there are any local adverse reactions to receiving a treatment. The majority of studies in this area have included between one and three attributes related to mode of administration in the design. As there are often multiple aspects related to the mode of administration, the approach taken varies between separating out all aspects into separate attributes, or presenting multiple aspects, for example, route of delivery and frequency of administration into the same attribute. The approach of presenting different types of treatment administration together is most common. Where multiple types of treatment delivery are presented together within an attribute they reflect a bundle of inseparable aspects which may be context and treatment specific. Studies published within the last 2 years have tended to separate out mode of administration attributes which allows better understanding of the influence of the different components.

Table 1 Studies evaluating preferences for mode of administration in rheumatological conditions

First Author	Year	Country	Method	Population	Treatment	Sample Size	Attributes (mode of administration in bold)
Augustovski [21]	2013	Argentina	DCE	Patients (naïve to biologics)	Rheumatoid Arthritis	240	Patient global assessment of disease activity Mode of administration Frequency of administration Local adverse events Generalized adverse events Serious infections Costs
Burnett [27]	2012	Canada	DCE	Parents (experienced)	Juvenile Idiopathic Arthritis	105	Child reported pain from arthritis Participation in daily activities Side effects Drug treatment Days missed from school Cost to you
Constantinescu [22]	2009	United States	ACA	Patients (experienced)	Rheumatoid Arthritis	136	Remission Improvement Radiographic progression Route Injection reaction Reversible adverse events Risk of lung injury Risk of tuberculosis Extremely rare adverse events Risk of cancer
Darba [14]	2011	Spain	DCE	Patients (experienced)	Osteoporosis	166	Type of administration Place of administration Cost
de Bekker-Grob [15]	2009	Netherlands	DCE	Patients (naïve); GPs	Osteoporosis	120 (patients), 40 (GPs)	Route of drug administration 10-year risk reduction of hip fracture Nausea Total treatment duration (years) Cost to you
Fraenkel [16]	2006	United States	ACA	Patients (132 experienced, 80 naive)	Osteoporosis	212	Route of drug administration 10-year risk reduction of hip fracture Nausea Total treatment duration (years) Cost to you Absolute risk reduction of vertebral fractures Risk of adverse effects
Fraenkel [17]	2006	United States	ACA	Patients (experienced)	Osteoporosis	76	Type of treatment Efficacy
Fraenkel [18]	2008	United States	ACA	Patients (experienced)	Osteoporosis	90	Route of administration Decrease in pain Improved strength

Table 1 (continued)

First Author	Year	Country	Method	Population	Treatment	Sample Size	Attributes (mode of administration in bold)
							Risk of dyspepsia Risk of bleeding ulcer
Fraenkel [26]	2014	United States	ACA	Outpatients (recruited from outpatient so experienced and naïve)	Osteoarthritis	304	Route of administration Expected benefit Risk of drug toxicity Cost
Harrison [23]	2015	Canada	DCE	General population	Rheumatoid Arthritis	733	Route of administration Frequency of administration Benefit Serious side effect Minor side effect Newness of the drug Life expectancy
Hiligsmann [19]	2014	Belgium	DCE	Patients with or at risk for (experienced and naïve)	Osteoporosis	257	Efficacy Cost per month Mode of administration Frequency of administration Side effects
Laba [20]	2013	Australia	DCE	Patients (experienced)	Osteoarthritis	188	Pain efficacy Mode of action Dose frequency Treatment schedule Cost Prescription Side effects
Ozdemir (12)	2009	United States	DCE	General population	Rheumatoid Arthritis	534	Chance that the medicine will work well If it works, how long it takes to work after you start taking the medicine Way that you take the medicine How long the injection site is irritated after taking the medicine Chance of getting a serious infection Personal cost to you per month not covered by insurance
Poulos [25]	2014	United States	DCE	Patients (RA group) and general population	Rheumatoid Arthritis	901	Chance of medicine working well Mode of administration Time needed for infusion How often injections/infusions are taken Chance of immediate serious treatment reaction Chance of immediate mild treatment reaction

Importance of Mode of Administration

Findings from published studies are equivocal about the importance of aspects of mode of administration in the decision making process (Table 2).

Route of Administration

The route of administration of a drug was found to be a significant factor in treatment decisions for people with RA, suggesting a preference for an oral (tablet) method of drug administration compared with an intravenous route [21]. In contrast, in a study eliciting societal preferences for similar treatments in the Canadian setting revealed significant preferences for oral routes versus intravenous infusions of treatments in respondents who had no previous experience of injected treatments, but no preference for those who had experienced injected treatment [23]. This suggests that preferences for a route of administration of a treatment may change over time or with experience of using different types of treatment. A study comparing intravenous infusions with injectable treatments found a small but non-significant coefficient in the direction of preference for injectable treatments; however, this attribute also included the location of treatment (injection at home and infusion at a doctor's office or clinic) [25].

In other settings within rheumatology, the evidence supporting preferences for less invasive treatment is more consistent. Studies aimed at understanding treatment decisions at the individual level in osteoporosis [18] and OA [26] found that between 9 and 60 % of treatment decisions were related to the route of administration [17, 18, 26]. The study reporting that 60 % of the treatment decision was influenced by route of administration was in the context of very different options, hip protectors and bisphosphonate medications for patients at high risk of osteoporotic fracture. In this setting, the mode of administration was considered more important than the potential treatment benefits (60 versus 40 %) [17]. Interestingly, preferences for hip protectors were higher (36 versus 19 %) in non-bisphosphonate users than in current bisphosphonate users [17]. In a similar study, but in those with knee OA, a wider range of treatment alternatives were compared (creams, tablets, injections into the knee, and exercise therapy) and in this setting the route of administration accounted for 24 % of the treatment decision [18]. In a further study of knee OA comparing the route of medication (pill, injection, infusion), on aggregate, route of administration accounted for only 9 % of importance in the treatment decision [26]. However, a small subgroup of patients (5 %) appeared to have preferences for treatments that were dominated by route of administration, approaching 60 % of importance [26]. This particular subgroup would only consider subcutaneous injections under a best-case scenario of other aspects of benefit, risks, and cost [26].

Frequency and Duration

Some studies have found the frequency and duration of treatment to be a significant driver of preferences for treatments. For example, more frequent administration of treatment, alongside other aspects of treatment, was found to significantly and negatively influence preferences of people with RA for biologic therapies [21, 25]. However, frequency of drug administration in the RA setting was not found to significantly influence societal treatment preferences for treatment alternatives [23]. In knee OA, the treatment schedule for analgesics, whether the treatment was given as needed or daily, was a significant factor in patient preferences about continuation of a treatment. Similarly, in RA a significant preference for the frequency of administration of biologic therapies has been reported [25]. In contrast, the frequency of dose, whether an analgesic was given once a day or three times a day, was not a significant factor [20]. In this context, the preference for schedule of treatment appears to reflect a preference for non-chronic drug treatment rather than convenience.

Route and Frequency/Duration

Where the mode and frequency of administration of treatments have been combined in a single attribute, there are a number of studies where this attribute significantly influences preferences for treatment [14, 15, 27]. RA patients appeared to prefer oral and subcutaneous routes of administration to intravenous infusions, and less frequent medicines to more frequent medicines, but the way these aspects were combined in an attribute makes the relative contribution of route and frequency difficult to interpret [24]. One study of osteoporosis suggested patients have preferences for daily subcutaneous injections to either daily or weekly oral drugs, or intravenous injections once a year, but again these preferences may reflect both the route and/or frequency of administration [14]. A study of decisions at the patient level among treatment-naïve (bisphosphonates) patients in osteoporosis indicated that almost two thirds of patients would prefer an annual infusion to oral weekly bisphosphonates [16]. In contrast, a further study in osteoporosis showed a preference in patients for a monthly tablet, compared with a weekly tablet or a weekly injection [15]. Interestingly, the same survey conducted in general practitioners found no preference for route of administration.

A sample of parents of children with JIA indicated preferences for avoiding intravenous treatments once per month compared to subcutaneous or oral administration of the drug four times per month, although only the subcutaneous route was statistically significant [27]. This particular attribute mixed route with frequency and the person who administered the drug treatment, but as only the reference category differed in frequency and who administered the drug, it was possible to

Table 2 Influence of mode of administration attributes on preferences in selected studies

First Author	Year	Mode of Administration Attribute(s)	Levels	Summary of Findings
Augustovski [21]	2013	Mode of administration Frequency of administration	Oral (ref) Subcutaneous Intravenous Every 10 months (ref) Every month Every week Every day	-Frequency and route of administration ranked third and fifth respectively out of seven attributes -Preference for less frequent administration -Preference for an oral tablet over intravenous infusion
Burnett [27]	2012	Drug treatment	Self- or parent-managed pill 4 days per month Self- or parent-managed injection 4 days per month Doctor- or nurse-managed IV 1 day per month	-Drug treatment ranked fifth out of six attributes -Preference for subcutaneous injection 4 days per month over monthly IV -Preference for pill over IV was not statistically significant
Constantinescu [22]	2009	Route Injection reaction	Pill you talk once a week Injection you give yourself once every 1–2 weeks Intravenous infusion you get every 6–8 weeks No injection reaction 30 of 100 people will have nausea, dizziness, or unusual tiredness 3 of 100 people will get a reaction during the infusion (headache, nausea, fever)	-Route of administration accounted for about 7–10 % of the importance in a treatment decision
Darba [14]	2011	Type of administration Place of administration	Subcutaneous injection (once daily) (ref) Oral (once daily or once a week) Intravenous infusion (once per year) medical support at home (ref) Self-administration hospitalization	-Patients were willing to pay 183€ per month for a daily subcutaneous injection over an annual intravenous injection -Patients were willing to pay 142€ per month for a daily subcutaneous injection over daily tablet -Patients were willing to pay 121€ per month to have medical support at home when administering the drug compared to being admitted to hospital -Patients were willing to pay 59€ per month to have medical support at home when administering the drug compared to self-administration
de Bekker-Grob [15]	2009	Route of drug administration	Tablet once a month (ref) Tablet once a week Injection by GP every 4 months Injection by GP every month	-Patients had significant negative preferences for tablet once a week, injection every 4 months, and injection once a month compared to a tablet once a month -GPs had significant negative preferences for injection once a month compared to tablet once a month
Fraenkel [16]	2006	Route of drug administration	A pill taken once a week Intravenous infusion administered over 2 h every 3 months Intravenous infusion administered over 15 min Once a year daily subcutaneous injection	-Route of administration accounted for 29.3 % of the total importance of the 4 attributes. -Among treatment-naïve participants 65 % preferred an annual infusion over oral weekly bisphosphonates
Fraenkel [17]	2006	Type of treatment	You take one pill once a week. You need to take the pill first thing in the morning before you eat. Side effects are uncommon, but may include stomach pain or heartburn	Mode of administration outweighed the potential treatment benefits (40 %)

Table 2 (continued)

First Author	Year	Mode of Administration Attribute(s)	Levels	Summary of Findings
			You wear a hip protector under your clothes every day. No added risk of side effects.	
Fraenkel [18]	2008	Route of administration	Cream applied on knee Pills Injection in the knee (up to four times per year) exercise	Mean relative importance of route of administration was 24.0 % which ranked higher than all other attributes
Fraenkel [26]	2014	Route of administration	A pill taken once a day Weekly subcutaneous injection Monthly infusion	-Route of administration accounted for 8.8 % out of the total relative importance of the five attributes -A small subgroup of patients (5 %) appeared to have preferences for treatments that were dominated by route of administration, approaching 60 % of importance -This subgroup would only consider subcutaneous injections under a best-case scenario of other aspects of benefit, risks, and cost
Harrison [23]	2015	Route of administration Frequency of administration	An oral medication (pill), taken wherever convenient, takes a few minutes A shallow injection under the skin, given by yourself (or someone you choose) wherever convenient, takes a few minutes IV/slow drip, given by a physician/nurse at their office/hospital, takes 3–4 h (ref) Twice daily (morning and evening) (ref) Once weekly Every 8 weeks	- No overall preference for oral drug administration compared with either subcutaneous injections or intravenous infusions - Subgroup analysis revealed significant preferences for oral routes versus intravenous infusions of treatments in those who were treatment naive, but none in those who were treatment experienced - Frequency of drug administration did not significantly influence treatment preferences
Hiligsmann [19]	2014	Mode of administration Frequency of administration	Oral Tablet Subcutaneous injection Intravenous injection Weekly Monthly Every 3 months Every 6 months Yearly	Patients WTP (per month) relative to weekly oral tablet: -Monthly oral tablet 16.16€ -Subcutaneous injection 3-monthly 4.24€ -Subcutaneous injection 6- monthly 19.53€ -Intravenous injection 3-monthly −15.28€ -Intravenous injection yearly 11.75€
Laba [20]	2013	Dose frequency Treatment schedule	1 time per day 3 times per day (ref) when needed (ref) daily	Patients were willing to accept AU$4.11 per month to switch from a treatment administered once daily to three times daily -This value was a fraction needed to accept a greater risk of side effects (AU$90 per month)
Ozdemir [25]	2009	Way you take the medicine Injection site irritation	1 injection every week at home (ref) 1 injection every 2 weeks at home 1 injection every 4 weeks at home 1 infusion every 8 weeks that takes 2 h in your doctor's office or clinic	-Location, route, and frequency were combined making the relative contributions difficult to determine. -Participants had a negative preference for 1 h of injection site irritation compared to 3 h, and a positive preference for 15 min compared to 3 h

Table 2 (continued)

First Author	Year	Mode of Administration Attribute(s)	Levels	Summary of Findings
			1 infusion every 12 weeks that takes 30 min in your doctor's office or clinic 15 min 1 h 3 h (ref)	
Poulos [25]	2014	Mode of administration Time needed for infusion How often injections/infusions are taken Chance of immediate serious treatment reaction Chance of immediate mild treatment reaction	Injection at home Infusion at a doctor's office or clinic No time (injection at home) 30 min 1 h 2 h 4 h 2 treatments every week (104 times per year) 1 treatment every 2 weeks (26 times per year) 1 treatment every month (12 times per year) 2 treatments 2 weeks apart every 6 months (4 times per year) 1 of 100 patients (1 %) 10 of 100 patients (10 %) 25 of 100 patients (25 %) 1 of 100 patients (1 %) 10 of 100 patients (10 %) 25 of 100 patients (25 %)	-Preference for injection over infusion -Negative preference for longer duration, and increase in treatment frequency -Negative preference for immediate mild and severe treatment reactions

indicate a preference for subcutaneous injections. Similarly, attributes in a DCE in osteoporosis combined route of administration and frequency in a single attribute, but in a way that allowed some understanding of the influence of length of dosing regimen and the route [19]. In this study, patients with osteoporosis were found to prefer a 6-month subcutaneous injection and a monthly oral tablet to a weekly oral tablet. The study failed to detect any significant preferences between an oral tablet every week, a subcutaneous injection every 3 months and an annual intravenous, or between subcutaneous injections every 6 months and an oral tablet per month. Irrespective of the route a drug was administered, it was found that patients preferred longer dosing regimens for any of the oral, subcutaneous or intravenous routes of administration.

At the individual treatment decision level, around 7–10 % of importance in a treatment decision for RA patients has been attributed to the route of administration between oral drugs and subcutaneous or intravenous injections, with varying frequencies of administration for these options [22].

Location of Administration

One study in rheumatology that considered the influence of location of administration for elderly patients with osteoporosis found significant preferences for self-administration in the home setting with medical support compared with administration at home without medical support or administration in the hospital setting [14]. However, it is unclear whether this is a preference for location or support in administering the drug.

Value of Mode of Administration Compared to Other Attributes

The relative importance of mode of administration compared with other health and non-health benefits of treatment has been reported in a number of studies (Table 2). In the single study in JIA, convenience (whether and how often the drug was orally or subcutaneously administered) ranked fifth out of six attributes, only higher than whether the child had to miss school, and lower than the child's level of participation in activities, pain, cost, and side effects [27].

In the study of osteoporosis that considered oral subcutaneous and intravenous administration and the hospital, medically supported or self-administration of treatment, the route of administration was found to be more important than the place of administration [14]. The estimates suggested a preference of the willingness to pay from this study suggested that patients would be willing to pay €142 per month for a subcutaneous injection once per day instead of a daily or weekly tablet, or €183 per month for a subcutaneous injection once a day rather than an intravenous injection once per year [14]. Estimates of the willingness to pay for medical support at home for self-administration at home ranged from €59 per month compared with self-administration at home with no medical support to €121 per month to move from administration at hospital to the home setting with medical support [14].

The value of route of administration has been quantified in RA in two studies. In the first, Hiligsmann et al. report that patients would be willing to pay €19.53 per month (or accept a reduction in efficacy of 13.5 %) to switch from a weekly oral to 6-month subcutaneous injectable delivery of treatment [19]. Further, patients were willing to pay €16.16 per month (or accept a reduction in efficacy of 10 % less) to change from a weekly oral to a monthly oral treatment. A move from an oral monthly treatment to a 3 monthly intravenous treatment would require a patient to be compensated €15.28 per month to accept treatment, or for the treatment to have a greater efficacy of 9 % or more to be accepted. Societal values on a life year scale suggested that respondents may be willing to trade off almost one third of a year (118 days) to have an oral drug compared with an intravenous infusion or one fifth of a year (148 days) to have an oral drug instead of a subcutaneous injection [23]. However, this study also reported these trade-offs may be temporary as people with experience of subcutaneous injections were not willing to trade any days for oral drugs.

The only estimates of the value of frequency of administration of a drug came from studies in OA and RA. In OA, it was that reported that patients would be willing to accept compensation of AU$4 per month to switch from a treatment administered once daily to three times daily [20]. This is a fraction of the compensation needed to accept a greater risk of side-effects (high blood pressure, heart/kidney/liver problems) (AU$90 per month) or a treatment that only relieved pain symptoms instead of slowing progression of OA (AU$14 per month). In RA, marginal rates of substitution suggested that reducing duration of treatment was more important than reducing frequency of treatment, for example, people would be willing to add two treatment sessions per year for a treatment schedule that reduced each treatment duration by 90 min [25]. The study also reported that a 1 h decrease in a quarterly infusion was valued 5 times more highly than a 1 % point improvement (from 60 % to 61 %) in the chance of the medication working well [25].

Issues and Recommendations in Measuring Values for Mode of Administration

In reviewing the evidence, we find most studies sought to identify if mode of administration has any value, but few go beyond this to look this in terms of actual monetary or health utility value placed on the attributes. Overall, we find three issues that seem pertinent for studies conducting research in this area.

Unit of Measurement

Many of the studies we reviewed reported values for convenience in terms of "utility" or willingness to avoid an event. While these can be useful for individual decision making and reflect the relative preferences for different aspects of treatment within a defined bundle of attributes, they can be difficult to interpret outside of the study. This is because the value only has meaning in context of the other treatment attributes. Studies that report willingness to pay overcome this limitation, by reporting in a unit, cost, that can be compared across contexts. However, there have been concerns about asking participants to trade-off costs in the health care context, since most people are unfamiliar with how much treatments and services really cost [28]. The study by Harrison et al. uses an alternative denominator by asking respondents to trade length of life—akin to a time trade-off study [23]. This enabled the authors to estimate values for inputting in to Quality-Adjusted Life Years (QALYs), the primary unit of measurement used to determine the cost-effectiveness of new treatments. This approach requires a larger sample size than many of the studies have included to facilitate a more complicated experimental design, but should be considered in future studies.

Attribute Selection

Stated preference studies are limited by the amount of attributes that can be included. Attributes relating to mode of administration need to be included alongside other attributes such as benefits and harms, and the literature suggests people struggle to compare more than 6 to 8 attributes [10]. Consequently, the studies we reviewed only included between one and three attributes relating to mode of administration. However, choosing what to include can be difficult since it is a multi-faceted concept including among others, differences in the place, frequency, route, and the person administering the treatment. There are also different factors which relate to different aspects of mode, for example, intravenous infusions may be perceived to be more convenient as you may receive treatments 6-months apart, but also less convenient as it is clear you need to have a health care professional to administer treatment, and there may be perceptions that you cannot withdraw from treatment in the event of adverse events as easily as the treatment is more long-acting multiple aspects get bundled together. Studies have tended to resolve this by bundling aspects together. This can be done explicitly where multiple aspects are described within a single attribute. However, this limits the interpretation since you cannot be sure which aspect is driving the effect, or whether the different aspects could have opposing effects which cancel or affect the magnitude of effect. It can also be done implicitly, whereby extensive background information describes not just the main aspect of the attribute (e.g., injection, infusion, or oral tablet), but also background information describing an infusion as being a treatment that requires a visit to a hospital that will take up to 3 h per visit, etc. In this situation, the apparent strength of effect for or against a particular attribute may be influenced by the background material. Future work should ensure that preliminary analysis is conducted to find the most important aspects relating to mode of administration in the particular context. We also recommend that all information provided to respondents is provided to help readers with interpretation, even if it is as an appendix [29].

Whose Values?

There is much debate on whose values should be used to judge the benefits of treatments for informing resource allocation decisions [30, 31]. To generate QALYs, is it is necessary to have some means of assigning a value to each patient's health state before and after an intervention. The SF-6D [32], and EQ-5D [33] are examples of preference based instruments which provide a means for patients to describe their health state using generic descriptions, and also provide a set of "societal" values for each of the possible health states depicted [34]. Although patients may be better at valuing their own health, most agencies that use QALYs have advocated that these values should be obtained from "a representative sample of fully informed members of the community - the general population"[31, 35, 36]. It is argued that societal values are better suited to inform policy decisions in publicly funded health care systems since they are behind a "veil of ignorance," and blind to their own self-interests [31]. Furthermore, focusing on the impact on health of an intervention assumes that healthcare itself has no positive value in use. While this assumption may or may not hold, it ignores the potential for the way healthcare is delivered having an impact on values, and might mean that less invasive interventions are preferred, a concept called process utility [37, 38]. While understanding preferences from a patient's perspective is crucial, we recommend future studies also ask representative members of the public to engage in preference tasks, so to inform policy makers of the value perceived from society.

Conclusion

Our synthesis of the evidence suggests that mode of administration for treatments in rheumatology is valued by both patients and society to some extent. The magnitude of this value is more challenging to elucidate, since the methods used in most studies do not allow for such comparisons. However, the context of the disease and the study participants appear to be important. Respondents with a more severe disease seem to give less value to mode and frequency of administration, since

improvement in pain and function are the priority. However, patients with chronic, but less severe, disease seem to place greater value on mode of administration. This may indicate that preferences in this latter group have not been properly formed, since experience with a disease and treatment often changes people's perceptions and values. It is, however, people with these less formed preferences that influence day to day decision making, and so may be one explanation for why rates of adherence to treatment tends to be more problematic in people with less severe disease. In terms of the participants, in the studies where patients with experience with treatments perceived to have less convenient modes of administration assigned lower values to more convenient treatments. This is consistent with findings in other disease areas [39] and can be explained by affective forecasting whereby people struggle to predict the impact of future unknown events [40]. Ultimately, whether payers should be paying a premium for treatments with more convenient modes of administration, but that provide no additional clinical benefit over existing treatments, depends on their normative objective toward resource allocation. Only through the generation of a greater evidence base on the value patients and the public assign to modes of administration can payers understand whether it contributes to their objectives or whether their objectives are aligned with the population they represent.

Acknowledgments Nick Bansback is a Canadian Institutes for Health Research New Investigator, Logan Trenaman holds a Canadian Institutes for Health Research Doctoral Award, and Mark Harrison holds a Professorship in Health Care Sustainability at the Faculty of Pharmaceutical Sciences, UBC.

Compliance with Ethics Guidelines

Conflict of Interest Nick Bansback, Logan Trenaman, and Mark Harrison declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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