

PREFERENCES FOR ROUTE OF ADMINISTRATION, FREQUENCY AND LOCATION

– A TIME-TRADE-OFF STUDY IN THE ITALIAN GENERAL POPULATION

Authors: Tine Rikke Jørgensen, Andrea Franchi, Filippo Lelli, Xin Ying Lee, Mette Bøgelund and Sarah Alulis (presenting author)

BACKGROUND AND OBJECTIVE

BACKGROUND

Medical treatments differ in many ways, including their clinical efficacy, safety profile, route of administration, where the treatments are given and administration frequency. Although the main focus is often on the clinical efficacy and safety profile, other elements may also play a significant role for the patients.

Different biologic treatments are administered differently. The frequency varies from every week to every 12 weeks. Some medications are given as infusions at the hospital and some as subcutaneous injections either at home or at the hospital.

OBJECTIVE

The objective of this study was to investigate to what extent the Italian general population have preferences for the type of treatment they potentially would receive, how often they would receive it and where. The study was prepared without reference to a disease and medication/brand names.

METHODS

PREFERENCES, QALY AND THE TTO METHODOLOGY

Comparisons of different treatments are crucial in the economic decision-making of the health care industry, especially when governments prioritize less costly treatments and determine the reimbursement status of different drugs. There are different ways of measuring people's preferences for different treatments. A common way is through utility, a term used in economic theory; utility is broadly synonymous with preferences.

Utilities are also commonly used to measure quality adjusted life years (QALYs), a measurement which combines quality and length of life. The quality of life comes from a utility measurement, and the length is the amount of years lived in a specific health state. One year has a utility weight range of 1 to 0, where 1 is equivalent to perfect health and 0 is equivalent to death.

Utilities and QALYs can be measured in different ways, but time-trade-off (TTO) is one of the most commonly used methodologies to elicit patient QALYs associated with a specific health state. The TTO is recommended by different governmental organizations, such as the UK NICE (National Institute of Clinical Excellence) and the Swedish TLV (Tandvårds- och läkemedelsförmånsverket) (NICE, 2013; TLV, 2003).

In the TTO, values are obtained by asking respondents to 'trade off' a portion of their remaining lifespan for an improved state of health. The TTO methodology was originally developed to elicit QALY values for hypothetical situations and has been validated against other utility eliciting measures (P Dolan, 1997; Paul Dolan, 1998; Paul Dolan, Gudex, Kind, & Williams, 1996; Paul Dolan & Jones-Lee, 1997; Robinson, Dolan, & Williams, 1997; G. Torrance, 1997; G. W. Torrance & Feeny, 1989; G. W. Torrance, Furlong, & Feeny, 2002).

HEALTH STATES

We identified eight health states that were different regarding where, how and how often the medication was given. The information was taken from the Summary of Product Characteristics (SPC) of commonly used biologic compounds. Since we were aiming at identifying steady health states, the maintenance doses were used instead of the initial doses. We included a warm-up health state to ensure that respondents had understood and familiarized themselves with the exercise. The eight health states are shown in Table 1 and correspond with the maintenance treatment regimens for a number of commonly used biologics (Figure 1).

TABLE 1 Health states

Health state	Where	How	Interval of weeks between treatment	Yearly frequency
1	Hospital	Subcutaneous	12	4.3
2	Home	Subcutaneous	12	4.3
3	Home	Subcutaneous	2	26
4	Home	Subcutaneous	1	52
5	Hospital	Infusion	4	13
6	Hospital	Subcutaneous	8	6.5
7	Home	Subcutaneous	8	6.5
8	Hospital	Infusion	8	6.5

FIGURE 1 Administration and frequency for selected biological treatment regimens



The subcutaneous injection and infusion descriptions were based on descriptions in patient information leaflets from products with the corresponding route of administration. We described the injection and infusion as if we were talking to an experienced patient that is used to being given an injection and infusion or giving it themselves. The respondent was instructed to assume that in all of the health states, their disease is well controlled by the medication and the only difference is in the route of administration, administration frequency and if they get their medication at home or in the hospital.

TYPE OF TREATMENT RECEIVED (AS DESCRIBED IN THE SURVEY)

A SUBCUTANEOUS INJECTION

A subcutaneous injection is an injection under the skin, with medication injected into your stomach or thigh. The injection is taken in a number of steps.

Take out the pre-filled injection device from the fridge approximately 30 minutes before injection. Wash your hands. Cleanse the skin with an alcohol wipe. Inject the medication into your stomach or thigh as instructed by your doctor/nurse. Press an antiseptic wipe and thereafter a cotton wipe over the injection site for 10 seconds.

The needle is quite thin and it does not hurt. A subcutaneous injection takes under 1 minute to complete. You may experience some pain at the injection site, sometimes with redness, itching and swelling.

AN INFUSION

An infusion is an intravenous way of providing medication – that is, through a drip into a vein in your arm.

The infusion is given in hospital by a trained member of staff. The hospital calculates and prepares the correct dose. You will be treated as a day patient and will be able to have the infusion while sitting in a chair, so you won't have to undress. A member of the staff will cleanse your skin with an alcohol wipe before inserting the needle with the medication.

Before the infusion you will get a medical check (about 30 minutes) and a nurse will give you a drug (usually steroids and antihistamines). You will also be required to pay approximately € 20.

The insertion of the needle into your vein can hurt a bit (corresponding to the feeling of having a blood sample taken). The infusion takes approximately 2 hours in total and does not hurt. You will have a small wound where the needle entered your vein and will be offered a bandage.

SURVEY

Data was collected through an internet-based survey using an existing panel of prospective participants provided by a market research company, an approach that has been successfully used by other groups (Chang, Collins, & Kerrigan, 2001; Lieu et al., 2009; Szende et al., 2010). The panel covers a representative sample of the general populations in Italy. Only people aged 18 years or more were approached.

All people who were contacted had previously agreed to participate in surveys via the internet. Various channels (web banners, telephone interviews and personal interviews) were used for panel recruitment to ensure that it remained representative. Prospective participants were approached by email, and participation was at their discretion. In addition, the anonymity of respondents was preserved throughout.

The electronic questionnaire was programmed using a commercial survey software package, and the survey itself was carried out in Italian.

The functionality of the questionnaire was validated in a pilot study of 478 respondents in the UK. Following the pilot study, a few minor adjustments were made to the questionnaire. The questionnaire was subsequently translated into Italian by a professional translator and validated/adjusted to the Italian setting.

Respondents were excluded if they failed a test question (if the respondent chose to live with the disease for a shorter time than with full health for a longer time) or did not accept the premise of the TTO questions.

In order to avoid respondent fatigue, respondents did not evaluate all health states, but were randomly assigned to answer questions about five health states each (and the warm-up health state):

- One health state of subcutaneous injection at home every 12 weeks
- One health state of subcutaneous injection at the hospital every 12 weeks
- Either one of the following groups: subcutaneous injection at home every two weeks, subcutaneous injection at home every one week and infusion at the hospital every four weeks OR subcutaneous injection at the hospital every eight weeks, subcutaneous injection at home every eight weeks and infusion at the hospital every eight weeks

In addition, respondents were required to answer demographic questions regarding their age, gender, employment, household and income.

HEALTH STATE DURATION AND INTERACTION

To make the trade-offs as realistic as possible, the time horizons used are based on each respondent's projected life expectancy, which were obtained using the country, age and gender of the respondent at the time of the study, and the most recent World Health Organization life tables (WHO, 2014).

To identify the point of indifference (where both options are equally acceptable), respondents were repeatedly asked trade-off questions, with only the number of years living in full health varying each time. This procedure followed a standard bisection methodology, using starting point of utility = 0.8 to reduce the utility value to an interval of 0.025. In the case where the respondents did not trade at all or traded a lot of life, extra questions were asked to identify the reasons why (either because of a valid reason or because they did not accept the premise of the TTO methodology).

STATISTICAL ANALYSIS

All statistical analyses were performed using SAS® version 9.4 statistical software.

A utility value was assigned to each health state based on each individual response, derived from the midpoint of the indifference interval elicited using the iterative procedure described above.

Due to the distribution of the individual responses being unknown and suspected to be abnormal, non-parametric bootstrapping was used to simulate standard errors and confidence intervals for the mean TTO values. The parameter's distribution was estimated by repeatedly resampling the original data set with replacements (Atkinson & Wilson, 1995; Briggs, Wonderling, & Mooney, 1997; Efron, 1981). For the present study, 10,000 iterations were performed.

RESULTS

Of the original 2,113 respondents from the general population who started the questionnaire, 2,006 (94.9%) completed it. A further 181 (9.0% of completed surveys) respondents were excluded for failing the test question and 278 (13.9%) were excluded because they did not have a valid utility value for all five health states. The final sample is based on 1,547 respondents, 48% of the respondents are male and the average age is 44 years.

The figures below show the respondents direct preferences for type of treatment (Figure 2-3). Respondents prefer subcutaneous injections to infusions and prefer to receive a subcutaneous injection at home, either by themselves or from a nurse. Only 11% prefer to receive the subcutaneous injection at the hospital.

FIGURE 2 Which treatment type would you prefer if you could choose (at a hospital)?

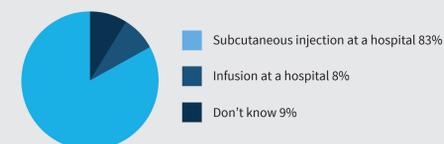
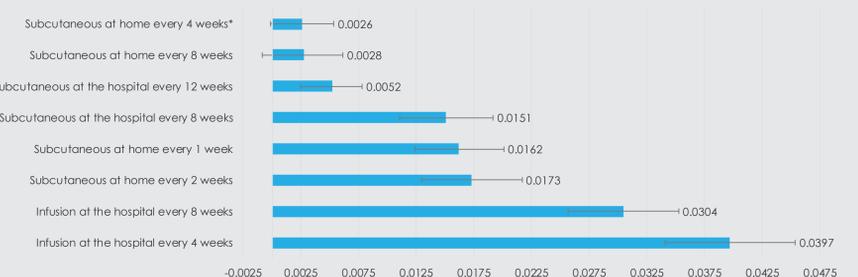


FIGURE 3 Which location would you prefer to get a subcutaneous injection if you could choose?



In the figure below (Figure 4), the results of various health states have been compared with the health state that the respondents consider to be the best: receiving a subcutaneous injection at home every 12 weeks.

FIGURE 4 Disutility from selected regimens compared with subcutaneous injections at home every 12 weeks



* Values were calculated based on a linear regression line using the four subcutaneous injection home health states.

All the seen differences are significant except the difference between subcutaneous injection every 4/8 and every 12 weeks.

STRENGTHS & LIMITATIONS

The web-based nature of this approach, whilst facilitating improved respondent participation and adaption, does have drawbacks regarding the lack of help available for respondents, should they require clarification regarding the exact nature of a question. Additionally, the lack of human supervision may have led to some respondents not spending enough time considering their answers before replying. Collectively, these design attributes may have led to inconsistencies and variations within the recorded responses. It should be noted, however, that the low dropout rate indicates that the questionnaire was clear and manageable for most respondents. Furthermore, electronic data collection avoids the risk of coding errors, as there is no need to enter the obtained data into a database that is needed for analyses.

Although participation bias must be considered, participants in the study received incentives to participate, which was expected to mitigate a respondent's disinclination to participate.

CONCLUSIONS

This study describes the application of a methodology to empirically derive the utilities associated with the route, frequency and location of administration, independent of the disease area.

The results show that route, frequency and location of administration matter for members of the general public as it has an impact on convenience. This study has also shown that the quality of life is better with a more convenient treatment regimen. When it comes to where and how the medication is given, there is a better quality of life associated with receiving subcutaneous injections at home. Receiving subcutaneous injections at the hospital is the second-best option, whereas receiving infusions at a hospital is associated with the lowest quality of life in this study.

Hence, the best health state is receiving a subcutaneous injection every 12 weeks at home.

Taking the patients' quality of life into account from medication, the side effects, frequency of medication, and mode of administration are important to maximize the quality of life for patients.

REFERENCES

(1) Atkinson, S. E., & Wilson, P. W. (1995). Comparing mean efficiency and productivity scores from small samples: A bootstrap methodology. *Journal of Productivity Analysis*, 6(2), 137–152. <https://doi.org/10.1007/BF01073408>

(2) Briggs, Wonderling, & Mooney. (1997). Pulling cost-effectiveness up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Econ*, 6, 327–340.

(3) Chang, W., Collins, E., & Kerrigan, C. (2001). An internet-based utility assessment of breast hypertrophy. *Plastic & Reconstructive Surgery*, 108(2), 370–7.

(4) Dolan, P. (1997). Aggregating health state valuations. *Journal of Health Economics*, 17(1), 39–52. [https://doi.org/10.1016/S0167-6296\(97\)00022-2](https://doi.org/10.1016/S0167-6296(97)00022-2)

(5) Dolan, P. (1998). The measurement of individual utility and social welfare. *Journal of Health Economics*, 17(1), 39–52. [https://doi.org/10.1016/S0167-6296\(97\)00022-2](https://doi.org/10.1016/S0167-6296(97)00022-2)

(6) Dolan, P., Gudex, C., Kind, P., & Williams, A. (1996). The time trade-off method: Results from a general population study. *Health Economics*, 5(2), 141–154. [https://doi.org/10.1002/\(SICI\)1099-1050\(199603\)5:2<141::AID-HEC189>3.0.CO;2-N](https://doi.org/10.1002/(SICI)1099-1050(199603)5:2<141::AID-HEC189>3.0.CO;2-N)

(7) Dolan, P., & Jones-Lee, M. (1997). The time trade-off: A note on the effect of lifetime reallocation of consumption and discounting. *Journal of Health Economics*, 16(6), 731–739. [https://doi.org/10.1016/S0167-6296\(97\)00051-0](https://doi.org/10.1016/S0167-6296(97)00051-0)

(8) Efron, B. (1981). Nonparametric Estimates of Standard Error: The Jackknife, the Bootstrap and Other Methods. *Biometrika*, 68(3), 589. <https://doi.org/10.2307/2335441>

(9) Lieu, T., Roy, G., Ortega-Sanchez, L., Kleinman, K., Rusinak, D., & Prosser, L. (2009). Willingness to pay for a QALY based on community member and patient preferences for temporary health states associated with herpes zoster. *Pharmacoeconomics*, 27(12), 1005–16. <https://doi.org/10.1185/03007995.2010.494126>

(10) NICE. (2013). Guide to the methods of technology appraisal.

(11) Robinson, A., Dolan, P., & Williams, A. (1997). Valuing health status using VAS and TTO: What lies behind the numbers? *Social Science & Medicine*, 45(8), 1289–1297. [https://doi.org/10.1016/S0277-9536\(97\)00057-9](https://doi.org/10.1016/S0277-9536(97)00057-9)

(12) Szende, A., Brazier, J., Schaefer, C., Deussen, R., Bitt, J., & Vyas, P. (2010). Measurement of utility values in the UK for health states related to immune thrombocytopenic purpura. *Current Medical Research & Opinion*, 26(8), 1895–903. <https://doi.org/10.1185/03007995.2010.494126>

(13) TLV. (2003). General guidelines for economic evaluations from the Pharmaceutical Benefits Board (LFNAR 2003:2).

(14) Torrance, G. W. (1997). Preferences for health outcomes and cost-utility analysis. *Journal of Managed Care*, 8–20.

(15) Torrance, G. W., & Feeny, D. (1989). Utilities and Quality-Adjusted Life Years. *International Journal of Technology Assessment in Health Care*, 5(4), 559–575. <https://doi.org/10.1017/S0264462300008461>

(16) Torrance, G. W., Furlong, W., & Feeny, D. (2002). Health utility estimation. *Expert Review of Pharmacoeconomics & Outcomes Research*, 2(2), 99–108. <https://doi.org/10.1586/14737167.2.2.99>

(17) WHO. (2014). Life Tables for WHO member states. Retrieved from <http://apps.who.int/gho/data/node.main.687?lang=en>