A Cost Utility Analysis Alongside a Cluster Randomised Trial Evaluating a Minor Ailment Service Compared to Usual Care in Community Pharmacy

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Abstract

Background

Minor ailments are "self-limiting conditions which may be diagnosed and managed without a medical intervention". A cluster randomised controlled trial (cRCT) was designed to evaluate the clinical, humanistic and economic outcomes of a Minor Ailment Service (MAS) in community pharmacy (CP) compared with usual care (UC).

Methods

The cRCT was conducted for six months from December 2017. The pharmacist-patient intervention consisted of a standardised face-to-face consultation on a web-based program using co-developed protocols, pharmacists’ training, practice change facilitators and patients’ educational material. Patients requesting a non-prescription medication (direct product request) or presenting minor ailments received MAS or UC and were followed-up by telephone 10-days after the consultation.

The primary economic outcomes were incremental cost-effectiveness ratio (ICER) of the service and health related quality of life (HRQoL). Total costs included health system, CPs and patient direct costs: health professionals’ consultation time, medication costs, pharmacists’ training costs, investment of the pharmacy and consultation costs within the ten days following the initial consultation. The HRQoL was obtained using the EuroQoL 5D-5L at the time of the consultation and at 10-days follow up. A sensitivity analysis was carried out using bootstrapping. There were two sub-group analyses undertaken, for symptom presentation and direct product requests, to evaluate possible differences.

Results

A total of 808 patients (323 MAS and 485 UC) were recruited in 27 CPs with 42 pharmacists (20 MAS and 22 UC). 64.7% (n=523) of patients responded to follow-up after their consultation in CP. MAS patients gained an additional 0.0003 QALYs (p=0.053). When considering only MAS patients presenting with symptoms, the ICER was 24,733€/QALY with a 47.4% probability of cost-effectiveness (willingness to pay of 25,000€/QALY). Although when considering patients presenting for a direct product request, MAS was the dominant strategy with a 93.69% probability of cost-effectiveness.

Conclusions

Expanding community pharmacists’ scope through MAS may benefit health systems. To be fully cost effective, MAS should not only include consultations arising from symptom presentation but also include an oversight of self-selected products by patients. MAS increase patient safety through the appropriate use of non-prescription medication and through the direct referral of patients to GP.

Trial registration

The study was not registered but it was approved by the University of Granada Ethics Committee (approval number 331/CEIH/2017) and Xátiva-Ontinyent Ethics Committee "Lluís Alcanyis".

Introduction

The World Health Organization (WHO) defines the pharmacy practice mission as “contributing to health improvement and helping patients with health problems to make the best use of their medicines”1. One of the six major components of this mission is identifying, managing and triaging health-related problems1. Minor ailments are defined as "common or self-limiting conditions which may be diagnosed and managed without a medical (i.e. doctor) intervention"2. Traditionally, patients present in community pharmacy (CP) for these conditions or alternatively self-select a non-prescription medication3. There are many countries where non-prescription medicines to symptomatically treat these minor ailments are exclusively available to the public through CPs1,4.
Minor ailment services (MASs) have been implemented in CPs in a number of countries as part of governments’ health policies. The objective is to promote CPs as a first point of call for minor ailments, encouraging patients to seek care at the appropriate level within the health system thus diminishing cost and allowing optimal use of health resources. A survey carried out in ten different countries in 2013 stated that 63% of the population in southern European countries consulted a general practitioner (GP) when suffering a minor ailment. Studies have estimated that the percentage of GP visits due to minor ailments vary between 18% to 31.2%, with 13.2% potentially manageable by CPs. Furthermore, the Australian Institute of Health and Welfare (AIHW) calculated that 7.5% of the emergency department (ED) visits in Australia in 2018-2019 were due to non-urgent visits (triage category 5). A study carried out in North East England estimated that up to 8% of ED workload is for minor ailment presentations that could potentially be managed in CP.

The economic impact of MAS has been previously compared to GP and ED settings. Across England and Scotland, studies have concluded that MASs release National Health Services (NHS) resources by redirecting care for minor ailments to lower costs settings such as CP with a total cost annual saving estimated to be approximately £1.1 billion (2013). In Canada, a pharmacist prescribing for minor ailment programs (PPMA) that addressed nine common minor ailments in the province of Ontario was estimated to save the health system more than $12.3 million. The Conference Board of Canada calculated a healthcare cost reduction, by using CP for treating minor ailments and administering vaccines, between $100 million and $200 million from avoided GP and ED visits. In an economic impact analysis in the province of Saskatchewan, PPMA resulted in an estimated health system cost saving of $546,832.

However, the cost utility or cost effectiveness of MAS compared to UC has been addressed in only one paper conducted in Australia. The researchers showed that MAS demonstrated cost effectiveness compared to UC with an incremental cost-effectiveness ratio (ICER) of $2,277 (95% CI, $681.49-3,811.22) (Australian dollars) per QALY.

The application of MAS to the Spanish health system requires local data to ensure transferability. Since no cost utility evaluations have been carried out comparing MAS to UC in Spain, a study was designed to evaluate the clinical, humanistic and economic outcomes of MAS compared with UC in CP. Humanistic and economic outcomes are reported in this paper.

**Methods**

**Study design**

The economic evaluation consisting of a cost utility analysis (CUA) was undertaken alongside a cluster randomised controlled trial (cRCT). The cRCT was conducted in Valencia (Spain) for six months between December 2017 and May 2018. The full report of the study in Spanish language is available.

**Participants**

The Pharmaceutical Association of Valencia provided CPs with study information via phone or email. CPs within twenty-one municipalities agreed to participate. The municipalities were the clusters of the study to avoid contamination between groups. Municipalities with pharmacies who accepted to participate were randomised through a sequence of computer-generated random numbers to the control (UC) and the MAS arms applying a ratio of 1:1. Due to the nature of the intervention, pharmacists could not be blinded.

Patients aged ≥ 16 years or over 2 years of age if they were accompanied by a responsible adult, who were seeking care i.e. presenting symptoms or requesting a product (direct product request) for the minor ailments were included in the study. The minor ailments considered in the study were: dermatological problems (cold sore, foot fungi), gastrointestinal disturbance (diarrhoea, flatulence, heartburn or vomiting), pain (dysmenorrhea, headache, sore throat) and upper respiratory tract (cough, cold or nasal congestion).
Description of the intervention (MAS)

The intervention is described using the TIDieR\textsuperscript{24} checklist (Additional file 1). The main components to the intervention being:

1. A standardised pharmacist–patient consultation\textsuperscript{25} using: co-developed with doctors management protocols for each specific symptom\textsuperscript{26}, patient educational material, and a web-based data collection software\textsuperscript{27} that guided pharmacists through the consultation with selected pop-ups such as referral criteria (i.e. “red flag symptoms”).

2. Practice change facilitation (PCF): PCFs made regular on-site visits to MAS CPs to identify and resolve barriers with service provision and check the fidelity of the intervention.

3. Educational training for MAS pharmacists was a twelve-hour training session delivered prior to the beginning of the trial. It covered service provision, good practice standards, service protocols, communication’s skills with the patient and other health professionals, web-based data collection software use, data collection and trial protocol.

The control group documented their usual practice and attended a three-hour training on data collection procedures and patient recruitment.

Study outcomes

Incremental cost-effectiveness ratio (ICER) of the service and health related quality of life (HRQoL) were the main outcomes.

Data collection was undertaken at the moment of the consultation in the CP (i.e. patient demographics, medicines supplied, HRQoL) using a web-based data collection software\textsuperscript{27}. Ten days after the consultation, patients were contacted by telephone by the research group to collect post consultation data. This follow-up time frame was considered appropriate given minor ailments are self-limiting conditions that should resolve within a short period of time. Patients self-reported HRQoL using EuroQoL 5D-5L self-complete version on paper at the time of the pharmacy consultation and 10 days later through telephone interview with a researcher using the EuroQoL 5D-5L telephone version\textsuperscript{28}.

In addition, the control group documented the consultation, which is not normally part of UC.

Sample size

Sample size calculation was based on the clinical primary study outcomes. A 10% absolute increase in appropriate medical referral rate (85% to 95%)\textsuperscript{29} and modification of direct product request (8% to 18%)\textsuperscript{30,31} were estimated. The sample size was calculated with \( \geq 0.9 \) power, type I error rate of 5%, equal allocation ratio and assuming an intra-cluster correlation of 0.01. The larger of the two-estimated sample size calculations was used to determine the overall sample size, of 726 patients (allowing for 10% dropout).

Statistical analysis and economic evaluation description

A descriptive analysis was performed to analyse baseline characteristics by group. Continuous variables were described using mean and standard deviation (SD) and categorical variables were presented as counts and percentages. Comparison of continuous variables between groups was undertaken using t-Student test and Kruskal-Wallis or Mann-Whitney (when skewed). Comparison of categorical variables was undertaken using Pearson’s \( \chi^2 \) tests. The level of statistical significance was established as \( p<0.05 \).

The research was reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Additional file 2)\textsuperscript{32}.

The effectiveness of the intervention was estimated as quality-adjusted life years (QALYs). QALYs were obtained from the cRCT\textsuperscript{23} with the HRQoL questionnaire administered at the time of the pharmacy consultation using the EuroQoL 5D-5L self-complete version on paper and at 10-day follow-up via the telephone interview version by the research team\textsuperscript{28}. Utility indexes
associated with each health state were taken from the published Spanish tariff\textsuperscript{33}. QALYs were calculated as area under the curve\textsuperscript{34} considering a 10-day time horizon for patient follow-up. Due to missing data in the sample in relation to the EQ-5D-5L data at follow-up, multiple imputation with chained equations was performed in order to allocate data. The multiple imputation missing data model included as predictive variables, EQ-5D-5L indices, at baseline and follow-up, and patient characteristics such as sex, age, and type of minor ailment (dermatological problems, gastrointestinal disturbance, pain and upper respiratory tract). Firstly, the missing data were imputed under the missing at random (MAR) assumption; this was the main analysis (base-case). Secondly, a completed case analysis was performed. It was assumed that patients who completed all follow-up are representative of the entire sample who initially agreed to participate) and assumes data are missing completely at random (MCAR). The utilities shown in both cases have been adjusted for age, gender, type of minor ailment, symptom duration and baseline utility. A simple pattern mixture model was implemented, following the approach recommended by Faria et al\textsuperscript{35}.

Total direct costs included costs to the health system, CPs and direct patient costs. Direct costs included the cost of health professionals’ consultation time, medication costs, pharmacists’ training costs and investment of the pharmacy (infrastructure, etc.) and costs of patients’ re-consultation in the following 10 days after initial consultation in CP (including contacts with all health providers such as GP and ED consultations). Medication costs, as out-of-pocket costs borne by the patient, were based on official prices listed in the Bot Plus® database at September 2018\textsuperscript{36}. CP consultation costs (for both groups) were calculated on time spent by pharmacists for the provision of the service, obtained from the pharmacists’ web-based data collection software for the cRCT. The unit cost of labour of the community pharmacist was calculated using the pharmacist’s salary as determined by the Spanish community pharmacy agreement\textsuperscript{37}. To calculate the costs related to the infrastructure investment and maintenance costs for the pharmacy, estimates were used from a previous Spanish study\textsuperscript{38}. Pharmacist training costs were for the twelve-hour course (classroom costs, presenter’s costs, travels and accommodation costs). GP (56.95€) and ED (105.27€) consultation costs were based on Valencian Law 20/2017\textsuperscript{39}.

In order to allocate the costs proportional to each patient, the mean cost of investment per pharmacy was divided by the mean estimated number of patients included in a potential MAS per CP. A study conducted by the General Pharmaceutical Council of Spain stated that 15-20% of patients attending community pharmacy presented with minor ailment symptoms or were self-selecting a medication for treatment of their symptoms\textsuperscript{40}. Five thousand four hundred patients were estimated to potentially access a CP MAS annually with an estimated of approximately 120 patients per day per CP\textsuperscript{41}. The investment of pharmacies in the UC group was assumed to be null.

Incremental cost and QALYs were calculated using bivariate regression. Cost and QALY were adjusted for sex, age, type of minor ailment, and QALYs were also adjusted for baseline utility to account for differences between groups at baseline. Coefficients were combined across the multiple imputed datasets using Rubin’s rules\textsuperscript{35}. To assess the robustness of the results, missing data models were performed.

Two sub-group analyses accounting for presentation type were performed were carried out to evaluate possible differences. This included patients presenting to the CP with symptoms or patients directly requesting a product.

Finally, a sensitivity analysis was carried out using bootstrapping. Uncertainty and the impact of varying the input parameters was measured through 1000 bootstrap. The probability of the intervention being cost-effective was calculated assuming data was bivariate and normally distributed\textsuperscript{42}. Since there is not a formal QALY monetary value assigned by the Valencian or National Spanish government, a study carried out by the government in Canary Island (Spain)\textsuperscript{43} was used for the assignment of a monetary value to the QALY. They suggested a willingness to pay per QALY from €20,000 to €25,000. All analyses were performed using STATA 14\textsuperscript{44}

Ethics
The study was approved by the University of Granada Ethics Committee (approval number 331/CEIH/2017) and Xátiva-Ontinyent Ethics Committee “Lluís Alcanyís”. Pharmacists provided written consent to participate in the study. Patients or responsible adults (when the patient was under age) who met eligibility criteria were requested to give consent after being informed of the aims of the study.

Results

A total of 808 patients (13 MAS and 14 UC) were recruited in 27 CPs with 42 pharmacists (20 MAS and 22 UC) (characteristics are included in Additional file 3). Most patients were female (63.1%, n=510), presented with upper respiratory tract symptoms (65.5%, n=529), had a symptom presentation (69.8%, n=564), presented symptoms suffered previously (91.6%, n=740) and had not treated their symptoms for this episode prior to visiting the pharmacy (78.8%, n=637). The mean patient age was 47.6 years old (SD=16.6). Statistical differences between groups were only found for baseline HRQoL (both utility and EQ-VAS); the MAS group presented a utility index of 0.87 (SD=0.12) compared to the UC group, of 0.89 (SD=0.14) (p<0.001). Patients visiting MAS pharmacies with direct product requests had lower baseline HRQoL (0.86, SD=0.11) compared with UC patients (0.90, SD=0.12) (p=0.020).

Health system, CPs and patient direct costs are presented in Table 1. Thirty pharmacists attended each training sessions and thus the cost per pharmacist was 272.20€ (overall training cost was 3090€/30 pharmacists), with pharmacist's time costing 169.20€. Approximately 5,400 patients were estimated to potentially access a CP MAS annually per pharmacy with a training cost per consultation of 0.05€. Training costs were only included for the MAS pharmacies.

The total infrastructure investment and maintenance costs were estimated to be €2,883.43 per year with a cost per consultation of 0.53€.

A total of 523 patients were followed up after consultation in CP (64.7% out of the 808 patients), 292 in UC pharmacies and 231 in MAS group. HRQoL was higher for those patients visiting MAS CPs with statistically significant differences found between groups at follow-up (p=0.053 without multiple imputation and p=0.042 with multiple imputation) (Table 2).

When considering completed cases, cost-effectiveness of MAS was 24,733€ per QALY with a 47.4% probability of cost-effectiveness using a willingness to pay of 25,000€/QALY (Table 3).

Thirty percent (n=244) of patients requested a product to self-medicate (Additional file 3). When cost-effectiveness was studied for these patients, MAS was the dominant strategy with a 93.69% probability of cost-effectiveness with a willingness to pay of 25,000€/QALY (Table 3).

Over one-third of the bootstrap simulations were located in the upper-right quadrant (36.19%) of the cost-effectiveness plane with a willingness to pay of 20,000€/QALY (Figure 1). When only considering direct product request presentation types, most of the bootstrap simulations were located under the threshold for a willingness to pay of 20,000€/QALY (92.60%) (Figure 3).

The acceptability curve shows that if the willingness to pay is 25,000€/QALY, the probability of MAS being cost effective, compared with UC, is 66.45% (Figure 4). It increases to 97.32% when considering only consultations due to direct product requests (Figure 6).

Discussion

This is the first study to evaluate cost utility for a MAS in Spanish CPs compared to UC. The results of the study showed that implementing MAS has clinical benefits for patients, resulting in higher HRQoL as shown in previous studies. A positive effect was obtained in HRQoL when a ten-day time horizon was contemplated. When considering multiple imputation, statistically significant differences were found for baseline HRQoL, between groups. When results were adjusted for baseline
HRQoL, statistical difference was found in favour of the MAS CPs. Although minor ailments are self-limiting, they may have an impact in patients’ daily life so patients’ perception of their health status can change in a relative short period. In addition, MAS allows the provision of additional information about conditions or medicines, and referral to other health care professionals when needed.

When studying consultation costs, medication expenses, paid directly by patients, accounted for the main costs of the consultation. Medication costs were similar in both groups. Pharmacists in the MAS group spent longer with the patient as would be expected due to the depth of the consultation. Total consultation costs (considering the first consultation in CP and any additional consultations within 10 days) was higher in the MAS group due to greater number of direct referrals to other health professionals. Increasing appropriate referral may improve patient’s safety.

The results showed an ICER of 24,733€/QALY due to the increase in QALY gain during ten days after the consultation in MAS CPs compared to the UC group. These results are higher than obtained internationally22 (AUD $2,277/ QALY) and may be due to follow-up occurring at 10 days in this study, and at 14-days in the Australian study. This may have affected complete resolution of certain minor ailments in which a higher increase in HRQoL was obtained.

MAS has proven to reduce GP consultations and decrease the number of patients presenting minor ailment symptoms at primary health care centers11. Our study results showed that it is important to extend this service to direct product requests since the evidence suggests that there is increase in HRQoL, cost effectiveness and patient safety. MAS pharmacists modified by 11.4%23 (compared to 4.5% in UC CP) the medication requested by the patients. Using the willingness to pay threshold of 25,000€, MAS was the dominant strategy with a 93.69% probability of cost-effectiveness for patients with direct product requests.

As shown in previous studies, consultations were performed differently when symptoms were presented than for a direct product request. When a patient presents with symptoms and is directly asking for advice, it provides an easier opportunity for the pharmacist to conduct a deeper consultation. The self-selection of the product by patient makes it challenging for pharmacists to intervene and in usual practice less advice is reportedly given to those patients,. It appears that CPs are more engaged when resolving symptom presentations than when dealing with product requests46,47. As this study showed, using protocols to deal with direct product requests has a greater effect on HRQoL, and therefore, MAS is more likely to be cost-effective than when only considering symptom presentations. Implementing quality standards in CP helps promote the safe and effective management of minor ailments1, and appropriate self-selection of non-prescription medications. MAS also limited the variability in community pharmacy consultations through training and the use of a standard process.

While this study only focussed on MAS versus UC, comparing MAS versus GP and ED visits in Spain would be valuable. The international literature suggests that implementing MAS may reduce the burden in GP and ED visits decreasing primary health spending15,17,18,19,21,22. In Spain, it has been suggested that CPs could help reduce primary care pressure through managing minor ailments. In Spain in 2018, 230.6 million GP consultation and 28.7 million ED consultations took place. Health expenditure in 2018 was 71,145 million € with only 14.6% (10,387 million €) intended to primary health care. A Spanish national study carried out in 2018 concluded that 86.8% of the population visited the GP during the 12 months before and 15.4% over 15 years old could not get an appointment with their GP on time. In Spain, GP consultations increased by 17% and by 18% for ED presentations between 1987 and 2017. Therefore, the implementation of MAS may lead to a more efficient use of the primary health care resources.

Methodological limitations

There are a number of methodological limitations for this study:

The study took place in the province of Valencia, limiting the generalizability of results to a national level. The number of patients lost to follow-up was 35.3% (n=279), although results obtained from completed cases and using multiple imputation were similar. It is interesting to note that double the number of MAS patients responded to follow-up ten days after the consultation, compared to the UC group. This may be due to the increased time spent with the patient during the MAS
consultation.
Data obtained for consultations to GP and ED that took place during the ten days after the initial consultation in CP were self-reported by the patient and not validated with official data. Future studies should contemplate the use of health system data to obtain a more reliable health system cost. PCFs costs were not included due to the limited time spent with community pharmacists and lack of reliable documentation.
The UC group was asked to document the consultation. Therefore, consultation time and consultation costs in the UC group may be overestimated.

Conclusion
This is the first Spanish study to evaluate the economic impact of a MAS in CP, obtaining similar results to those carried out internationally. The overall findings showed that there is significant potential to adopt a MAS in Spain with an addition of including direct product request so that it has a higher impact on the health system. MAS may add further economic benefits due to the appropriateness of self-medication with non-prescription medicines. Expanding community pharmacists’ scope through MAS may benefit health systems; therefore, the contribution by CPs to this aspect of primary health care should not be underestimated.

Abbreviations
AIHW: Australian Institute of Health and Welfare
CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CP: Community pharmacy
CRCT: Cluster randomised controlled trial
CUA: Cost utility analysis
ED: Emergency department
FIP: International Pharmaceutical Federation
GP: General medical practitioner
HRQoL: Health related quality of life
ICER: Incremental cost-effectiveness ratio
MAR: Missing at random
MAS: Minor ailment service
MCAR: Missing completely at random
NHS: National Health Services
PCF: Practice change facilitation
PPMA: Pharmacist prescribing for minor ailment programs
QALY: Quality-adjusted life years
SD: Standard deviation
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Tables

Table 1. Summary of identified health resources and cost estimates

|                              | MAS CP* (n=323) | UC CP* (n=485) | P-value |
|------------------------------|-----------------|----------------|---------|
| Medication cost‡             | 7.67 (2.62)     | 7.88 (3.11)    | 0.331   |
| Consultation cost§           | 1.55 (0.95)     | 1.13 (1.05)    | 0.000   |
| Training cost                | 0.05 (0.00)     | 0.00 (0.00)    | NA      |
| Infrastructure and maintenance cost | 0.53 (0.00) | 0.53 (0.00)    | NA      |
| Total cost consultation in CP| 9.80 (3.37)     | 9.54 (4.07)    | 0.012   |
| Cost of other visits to GP or ED | 11.61 (13.19) | 4.94 (9.35)    | 0.001   |
| Total cost†                  | 21.41 (30.39)   | 14.48 (23.38)  | 0.001   |

* UC CP: Usual Care Community Pharmacy; MAS CP: Minor Ailment Service Community Pharmacy
† SD: Standard Deviation
‡ In Spain, medication costs are paid by the patient
§ Considering pharmacist role (supervisor/regular pharmacist): time used for pharmacist-patient consultation was 8.00 minutes (SD=2.45) for a supervisor in MAS group, 5.35 minutes (SD=3.20) for a regular pharmacist in MAS group, 6.57 minutes (SD=3.90) for a supervisor in UC group and 4.95 minutes (SD=3.85) for a regular pharmacist in UC group. Pharmacists in UC group were asked to document the consultation which is not part of usual care
★First consultation in CP and other consultations during the 10 days studied were considered
NA: Not applicable

Table 2. EuroQoL 5D-5L scores (adjusted)
| ALTERNATIVES                  | GROUP               | Number with missing baseline data | EQ-5D-5L baseline mean (SD†) ‡ | Number with missing data at 10 days | EQ-5D-5L at 10 days mean (SD†) ‡ |
|------------------------------|---------------------|-----------------------------------|---------------------------------|-------------------------------------|---------------------------------|
| Without multiple imputation | UC CP* (n=285)      | 0                                 | 0.911 (0.010)                   | 200                                 | 0.921 (0.011)                   |
|                              | MAS CP* (n=224)     | 2                                 | 0.891 (0.011)                   | 101                                 | 0.922 (0.013)                   |
|                              | P value             |                                   | 0.170                           |                                     | 0.053                           |
| With multiple imputation     | UC CP* (n=285)      | 0                                 | 0.900 (0.008)                   | 0                                   | 0.917 (0.018)                   |
| (base case)                  | MAS CP* (n=222)     | 0                                 | 0.881 (0.009)                   | 0                                   | 0.926 (0.014)                   |
|                              | P value             | 0                                 | 0.051                           |                                     | 0.042                           |

* UC CP: Usual Care Community Pharmacy; MAS CP: Minor Ailment Service Community Pharmacy

† SD: Standard Deviation

‡ Adjusted by patient’s age and gender, minor ailment and symptom duration and baseline utility

Table 3. Cost effectiveness analysis MAS CP vs. UC CP. Effectiveness measured as QALY.
| Sample Type                                | Total Cost† (mean) | Cost Diff | QALY† Diff | QALY Diff | ICER (€/QALY) | Probability of cost effectiveness |
|--------------------------------------------|-------------------|-----------|------------|-----------|---------------|----------------------------------|
|                                            |                   |           |            |           |               | WTP 20,000€ WTP 25,000€ WTP 30,000|
| All sample                                 |                   |           |            |           |               |                                  |
| Multiple imputation (base case)            |                   |           |            |           |               |                                  |
| UC CP*                                     | 10.68             |           |            |           | 0.0246        |                                  |
| MAS CP*                                    | 17.19             | 6.51      | 0.0247     | 0.0003    | 19,325        | 52.39% 66.45% 75.36%             |
| Completed Cases                            |                   |           |            |           |               |                                  |
| UC CP*                                     | 12.61             |           |            |           | 0.0245        |                                  |
| MAS CP*                                    | 20.03             | 7.42      | 0.0248     | 0.0003    | 24,733        | 36.19% 47.40% 60.10%             |
| Sample with symptom presentation           |                   |           |            |           |               |                                  |
| Multiple imputation                        |                   |           |            |           |               |                                  |
| UC CP*                                     | 10.35             |           |            |           | 0.0245        |                                  |
| MAS CP*                                    | 19.48             | 9.13      | 0.0247     | 0.0002    | 42,322        | 14.09% 23.92% 33.15%             |
| Completed Cases                            |                   |           |            |           |               |                                  |
| UC CP*                                     | 12.59             |           |            |           | 0.0245        |                                  |
| MAS CP*                                    | 22.97             | 10.45     | 0.0248     | 0.0002    | 48,126        | 11.20% 17.39% 24.40%             |
| Sample with direct product request         |                   |           |            |           |               |                                  |
| Multiple imputation                        |                   |           |            |           |               |                                  |
| UC CP*                                     | 11.59             |           |            |           | 0.0242        |                                  |
| MAS CP*                                    | 11.90             | 0.31      | 0.0248     | 0.0006    | 523           | 96.83% 97.32% 97.58%             |
| Completed Cases                            |                   |           |            |           |               |                                  |
| UC CP*                                     | 14.25             |           |            |           | 0.0247        |                                  |
| MAS CP*                                    | 13.54             | -0.71     | 0.0249     | 0.0006    | Dominant      | 92.60% 93.69% 94.49%             |

* UC CP: Usual Care Community Pharmacy; MAS CP: Minor Ailment Service Community Pharmacy

† Adjusted by patient's age and gender, minor ailment, symptom duration and QALY at baseline (first consultation in CP and other consultations such as GP or ED visits during the 10 days studied were considered)