Universitat de Girona
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QUALITY IMPROVEMENT in ASA PRESCRIPTION in PRIMARY HEALTH CARE

> BACHELOR'S THESIS

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1. LIST *of* ABBREVIATIONS.

>> TABLE 0. **ABBREVIATIONS.**

CONCEPT	ABBREVIATION
Advanced chronic ill patients	ACIP
The Spanish Agency of Medicines and Medical Devices *(Agencia Española de Medicamentos y Productos Sanitarios)*	AEMPS
Acetylsalicylic acid	ASA
Adverse side effects	ASE
Anatomical Therapeutic Chemical Classification System	ATC
Basic health area *(Àrea bàsica de salut)*	BHA
Catalan Health Service *(Servei Català de la Salut)*	CatSalut
Complex chronic patient	CCP
Cyclooxygenase	COX
Clinical trial	CT
Catalan Institute of Health *(Institut Català de la Salut)*	ICS
Medication related problems	MRP
Number needed to harm	NNH
Number needed to treat	NNT
Old-dependency age ratio	OADR
Primary health team *(Equip d'atenció primària)*	PHT
Potentially inappropriate prescribing	PIP
Potentially inadequate medications	PIM
Prostaglandin	PG
Potential prescribing omission	PPO
Randomized clinical trial	RCT
Thromboxanes	TX

2. ABSTRACT.

TITLE.

Quality improvement in ASA prescription in primary health care.

BACKGROUND.

Potentially inappropriate prescribing (PIP) in above 65 years old community-dwelling population is common and may result in adverse drug effects, hospitalisations and increased morbidity. Interventions using explicit or implicit criteria, which are time-consuming and complex, so as to tackle PIP have not been proven useful. Unjustified acetylsalicylic acid (ASA) prescription in our setting is relatively common and no strategy has been implemented to deal with it. Plus, there is no data whether this wrong indication is due to a real inadequate prescription or a clinical registry deficiency.

OBJECTIVES.

To assess the effectiveness of a short, defined and groupal educational intervention on unjustified ASA prescription in above 65 years old population in a primary health care setting, by measuring the percentage of ASA inappropriateness before and after the intervention in this segment of population. Secondary objectives are to analyse whether the potential decrease in ASA inadequacy prescription after the intervention is due to the fact that ASA had not been well-prescribed and it is a PIP or it is owing to the fact it has not been correctly registered in clinical record. We also aim to figure out which is the covariate that influences the most in reducing unjustified ASA prescription.

METHODS.

A community intervention trial will be performed in 26 primary health teams (PHT) across Girona health region, in which 15 of them will receive an educational intervention on unjustified ASA and the resting PHT will not, being control groups. PHT clusters will be randomised according to their type (rural or urban) and within each of these blocks, according to their average income tercile.

The feasibility of the educational intervention will be tested before executing the trial, by performing a pilot intervention. Intervention and control groups will be also compared to a national contemporaneous control group.

KEYWORDS.

Potentially inappropriate prescribing, primary health care, randomized controlled trial, acetylsalycilic acid prescription.

3. INTRODUCTION.

3.1 A DEMOGRAPHIC SHIFT.

The world's population is estimated to continue growing, despite doing so at a slower pace than in other periods of history owing to the reductions in mortality at all ages and fertility changes. Whilst Sub-Saharan Africa and the vast majority of Asia will account for most of the growth of the world's population, other world's regions will tend to shrink its population by the 2100, such as Europe and Northern America, due to several factors. Mainly, low levels of fertility as well as increased longevity will make these two regions have an older population. As a matter of fact, the growth rhythm of the number of people aged above 80 years is faster than ever: while in 1990 there were 54 million people in our globe, in 2019 this number has tripled to 143 million and is expected to reach 426 million in 2050 and 881 million in 2100. In 2019, 38 per cent of those above 80 years of age were living in Europe and North America. [1]

Regarding our territory, Spain had 9.183.000 people aged over 65 years in 2019, while in 2050 there will be 16.062.000. When taking into consideration the whole population, in 2050 a 36,8% of the Spanish population will be over 65 years, while nowadays it is only 19,6%. Furthermore, if we take into consideration estimations of old-age dependency ratios[1], our country is set to have the third highest OADR in the world, only below Japan and the Republic of Korea (78,4). [2]

Life expectancy at birth in our country has been between 2010 and 2015, 79,6 and 85,3 years for men and women, respectively. In comparison with the rest of the Southern European countries, Spain is 1,2 years in men and 1,5 years in women ahead of the mean life expectancy. Life expectancy is also estimated to keep on rising and by 2028, it is expected to reach 82,2 and 87,1 in men and women respectively and, by 2048, 84,8 and 89,3 years respectively. [3]

[1] Number of persons aged 65 years or over per 100 persons aged 20 to 64 years. It is one of the most commonly used indicators for monitoring changes in the age structure of populations.

Increase in life expectancy is, without a shadow of doubt, a success of our society. Likewise, a greater ageing of the population implies a higher vulnerability to several diseases related to this physiologic process.

Prevalence of multimorbidity, thus, increases importantly with age and tends to be present in the majority of people aged above 65 years. [4] Plus, multimorbidity is more common in females and in those living in a deprived area. They tend to have shorter life expectancies and a worse self-assessed health. [5] These patients have a worse functional status, quality of life and health outcomes and they tend to be higher users of ambulatory and inpatient care than those without multimorbidity. [6, 7]

3.2 POLYPHARMACY AND OLDER PATIENTS.

Prescribing for older people is challenging: age-related changes in body composition and multimorbidity are important factors. However, finding a balance between treating pathologies, whilst, at the same time, avoiding medication-related harm is also difficult for healthcare providers.

Thus, as stated before, aging implies, along with an impaired mechanism of adaptation and homeostasis, a change in pharmacokinetics and pharmacodynamics. [8]

The following table summaries pharmacokinetic changes in older people:

>> TABLE 1. PHARMACOKINETIC CHANGES IN OLDER PEOPLE.

PHARMACOKINETIC PROCESS	PHYSIOLOGICAL CHANGE	PHARMACOKINETIC EFFECT	EXAMPLES
ABSORTION	Increased gastric pH Slowed gastric emptying Decrease of gastrointestinal blood flow Alteration of intestinal motility	Slightly decreased absorption	-
DISTRIBUTION	Decreased total body mass Increased proportion of body fat Decreased proportion of body water Decreased albumin Increased alpha-1 acid glycoprotein	Increased apparent volume of distribution of highly lipid soluble drugs Decreased apparent volume of distribution of hydrophilic drugs	Benzodiazepines Morphine Amiodarone
METABOLISM	Reduced hepatic mass Reduced hepatic blood flow Reduced metabolic capacity	Less effective first pass metabolism and phase I	Lidocaine Propranolol Pethidine
EXCRETION	Reduced glomerular filtration rate Reduced tubular function and renal blood flow	Decrease in renal cleared water-soluble drugs	Digoxin, Gentamicin Litium, ACE inhibitors

DATA SOURCE: Adapted from *Mukhtar et al*, Drug therapies in older adults [8]

Pharmacodynamics are also altered. Elderly have a lower response to beta-blockers, furosemide and beta-agonists. On the other hand, they are more sensitive to certain medications, such as benzodiazepines (midazolam, diazepam), opioids, metoclopramide, dopamine agonists, L-DOPA, neuroleptics and oral anticoagulants. Furthermore, homeostatic alterations produced by ageing may alter the response to medications: from dysfunction of autonomic nervous system (bladder dysfunction, orthostatism), thermoregulation alterations, cognitive dysfunction, among others.

POLYPHARMACY is the concurrent use of multiple medications. There is not a universal definition, the number of medicines used to define it is arbitrary. It is usually applied to those patients who take five or more medications. However, whilst traditional, over-the-counter and complementary medicines are still in discussion whether they should be included in this definition, whenever we want to reduce medication-related harm, it is advisable to verify whether this patient take these or not. [9]
Polypharmacy is not necessarily negative: it may be appropriate or inappropriate/ problematic.

APPROPRIATE POLYPHARMACY refers to prescribing for a person with complex diseases or multiple conditions, in which medicines have been optimized and are prescribed according to best evidence. For instance, the prescription of secondary prevention medications for MI, which requires a combination of different classes of drugs (beta-blockers, ACE inhibitors, statins, antiplatelets).

On the other hand, **INAPPROPRIATE POLYPHARMACY** is defined as prescribing multiple medications inappropriately: the risk of harm outweighs benefit, the medicines burden is unacceptable to the patient, adherence is not being achieved and the combination of medications may create interactions or prescribed medicines treat the ADE of other medicines. [10] Inappropriate polypharmacy in older people could be defined as prescribing medications or certain medication groups in 65 years or older people, either because they are not effective or they entail a unnecessary high risk for older people when there is a safer alternative. [11]

Thus, **potentially inappropriate prescribing** definition **(PIP)** includes the term **potentially inappropriate medicines (PIM)** and **potentially prescribing omissions (PPO).** A PIM may imply a potential important risk of adverse drug events (ADE) and PPO entails the omission of a certain medicine which is clinically indicated for a determined disease or prevention. [12]

Polypharmacy in our environment is considerable: data show that in 2011/2012 in Spain, a 36,37% of 65 years or older patients were polymedicated, that is taking 4 or more medications, being analgesics and antihypertensives the most commonly used medication groups. [13] Research in other countries has shown similar data, such as Ireland with a 27% [14] or the USA with a 39%. [15]

Over the years, polypharmacy is increasing: a Scottish research team, for instance, analysed the number of community-dispensed medications in a specific health region between 1995 and 2010. They concluded that in 2010, the proportion of adults who had been dispensed more than 5 medications had doubled in relation to 1995, as well as the proportion of those who had been dispensed more than 10 drugs, which had tripled in 2010. [16]

The causes of polypharmacy are multiple. Undoubtedly, the ageing of population and its consequent multimorbidity imply a need for intaking multiple medications by older people. However, there are more factors. The vast majority of medical guidelines and, traditionally medical research, do not take into account patient factors' such as older age, multimorbidity, the presence of a dominant condition, frailty or the approach of the end of their lives. [17] In fact, multimorbidity and polypharmacy are typically exclusion criteria to participate in RCT [18].

Furthermore, single-disease guidelines recommend the initiation of medication to manage long-term conditions, becoming increasingly complex, and do not explain when medication should be stopped or reduced [19, 20]. Following several guidelines for different diseases of a same patient may be dangerous, since potentially drug-drug interactions have been found to be relatively common in several UK guidelines [21]. All in all, the implementation of these guidelines may increase the risk of adverse drugs effects and, at the end, be harmful.

The relationship between polypharmacy and socioeconomic status is still unclear. There are studies which relate low education level and polimedication [22, 23], whilst others do not

find consistent data on it. [24] In fact, a study found that old educated women were more likely to engage in polypharmaceutical consumption. [25]

Oldest old patients, those patients over 80 or 85 years old are one of the fastest growing segments of the population in the Western World.
They use more health services, have more chronic conditions and are high users of polypharmacy compared with younger elder patients. [26] However, in spite of this, they are either barely included in RCT because of their frailty and comorbidities. [27]
The beginning of prescribing cascades [28] is also a cause of polypharmacy. A prescribing cascade starts when a medication is prescribed and an ADE takes place, which is misunderstood as a new medical condition. So as to treat this new disease, a second drug is prescribed to treat this ADE. An example of this phenomenon would be the intake of a cholinesterase inhibitor to manage dementia, the development of urinary continence as an ADE with the subsequent prescription of anticholinergic drugs. Prescribing cascades also may take place with the intake of supplements, over-the-counter therapy or even medical devices.

Thus, we can identify these cascades by asking ourselves 3 questions [29]:

- *Before starting a medication or procedure to treat a medical condition*: Could this be an ADE?
- Is the initial drug therapy that led to the prescribing cascade needed? Could the dose be reduced? Could the drug be substituted for a safer alternative?
- Which could be the harms if the medication that led to the cascade is continued?

Tsoi C.S et al [30] described the prevalence of most prescribed medications and medical conditions in this segment of population in their health area in Canada and it turned out that only 3 of the top 10 medication classes were prescribed for symptom relief. The remaining medications were prescribed for risk factor modification.
However, medications for risk modification in such elderly patients may not have sense and might even be harmful: there is no evidence in this age group to support the efficacy of risk-modifying medications. Conversely, this effort might be harmful since it can worsen the

quality of life and make older people get confused since medication patterns tend to be complex.
The same author also stresses the heterogeneity of these patients and the importance of not placing this segment of population under the same umbrella, just as we would not do with their younger counterparts.

Inappropriate polypharmacy implies, as well, a big expense, approximately 18 billion US dollars worldwide. In other words, a 0,3% of global total health expenditure. [31] So as to tackle this specific problem, among others, the same report advised the Dutch Government to *a) Invest in medical audits targeting elderly patients, b) Support greater role of pharmacists to manage medicines for patients and to foster collaboration with doctors for revision and*
c) Encourage use of risk stratification process to identify patients and prepare targeted medicines management plan.

ADE, in fact, in some countries, are estimated to represent a 6-7% of all hospital admissions, being over two thirds of these avoidable. [32, 33] Hospital admissions by older people seem to be ADE-associated in nearly a third of the cases, being non-compliance, omission or cessation of medication the most ADE-related reason. [34]

If we take data from an alike national health system, a study conducted in England in 2015-2016 estimated that medication errors cost 98,5 million pounds annually to the system. The majority of medication errors had none or little potential for harm (72%) and 2% had potential to cause important harm. [35]

Regarding our country, 65 years or older people consume more than a 30% of daily prescribed medications for chronic diseases in Spain [36], accounting a 75% of total pharmaceutical expenditure in our country. [37]

Therefore, the aim of healthcare providers ought to ensure appropriate polypharmacy, that is, to make sure that the prescription of several medicines is rational and based on evidence, as well as taking into account the individual context of the patient. At the same time, the healthcare provider should attempt to reduce inappropriate polypharmacy.

In 2016 the National Institute for Health and Clinical Excellence published some recommendations on how to approach patients with multimorbidity, in which it underlines the importance of individualization plans and reviewing medicines and other treatments. [38]

As a matter of fact, the World Health Organization, through its third Patient Safety Programme [2], which is centered on the theme of medication safety, called member states to consider policies for regular, holistic medication reviews for patients taking multiple medications, to address appropriate polypharmacy at the point of medications initiation, during medication review and at care transitions, among other points. All in all, polypharmacy is a major problem in our environment and addressing it is a high priority, according to this organism.

3.3 TACKLING POLYPHARMACY.

Prescribing for older people is challenging and tackling polypharmacy is complex: comorbidities, age-related changes in pharmacokinetics and pharmacodynamics, physical deterioration...

Optimisation and, if possible, deprescription is a good start. Medical optimisation or deprescription are examples of quaternary prevention, which are those measures that prevent, diminish or relieve the harm caused by sanitary activities. [39]

DEPRESCRIPTION is the process of intentionally stopping a medication or reducing its dose to improve the person's health or reduce ASE.

Deprescribing is challenging and unique in every situation, since people taking the same medication and suffering from the same conditions may be influenced by different experiences, opinions, genetics…

Deprescription is not a mere act of stopping a medication or aiming to reduce the number of them, but an holistic exercise.

Paradoxically, PPO are prevalent in older populations and they associated with polypharmacy [40, 41]. This is probably due to the fact that family medicine physicians are reluctant to prescribe additional medications for patients already polymedicated because of

interactions, adherence or medications regimens. Thus, a risk/treatment mismatch has been proven: those patients which have the highest risk of complications have less probabilities to receive the recommended medication.

Moreover, patient-centred interventions, that involve the patient in the deprescribing process, tend to be more effective than those that do not count with him/her actively participating in it. [42] Not only clinical, but also psychological, social, financial and physical determinants should be considered when carrying out a deprescribing intervention. Todd et al described these determinants as the deprescribing rainbow, which depicts the heterogeneity of elderly patients and the relevance of taking into consideration the diversity and individuality of them [43]. Several examples of these determinants may be consulted in [>> ANNEX 1].

Owing to this above-mentioned complexity that dealing with deprescription has, several strategies have been developed so as to help the healthcare provider identify the inappropriate polypharmacy and support them in decreasing or stopping medications.

On one hand, several tools have also been developed so as to assess those medicines which are potentially inappropriate for elderly and, thus, should be avoided. These tools take into account implicit or explicit criteria [44]:

EXPLICIT CRITERIA are based on a list of medicines that have been considered inappropriate for elderly by a bibliographic revision and expert consensus methods. These measures tend to be oriented to the medication and the disease itself and may be applied with little or none clinical judgement.

- Beers Criteria 2019 (USA)
- Deprescribing guidelines and algorithms (Canada)
- FORTA, PRISCUS (Germany)
- STOPP/START (Ireland)

IMPLICIT CRITERIA, however, are based on the patient's information. They tend to be more sensitive and the patient's preferences may be included. Nonetheless, they are more time-consuming, they depend on the knowledge of the patient and might have low reliability.

- MAI - Medication Appropriateness Index
- 7 steps and polypharmacy app (Scotland)
- NO TEARS (Wales)

In fact, 3 of the most used criteria (MAI, Beers and STOPP/START) detect different prevalences of PIP and have different sensitivities. A recent Spanish study analysed PIP prevalence in community-dwelling population with multimorbidity and polypharmacy aged between 65 and 74 years old based on Beers 2015, Beers 2019, STOPP 2014 and STOPP 2008, having MAI as a gold standard [45]. Out of these criteria, Beers 2015 turned out to be the most sensible criteria to detect PIP, followed by its 2019 version. Thus, the use of these tools may be complementary and according to the purpose of its use and setting, we can use one or another.

When analysing the prevalence of PIP in Spanish community-dwelling population aged between 65 and 74 years based on 2014 STOPP criteria, it was found that 57% presented at least 1 PIP, being the most frequently found the prolonged use of benzodiazepines (36,6%). When using Beers criteria, nearly a 69% met at least one of the criteria, being the prolonged use of proton-pump inhibitors (nearly a 44%) the most common PIP.

However, there are other available strategies, such as SAIL and TIDE mnemonics, coined by Werder et al. [46], in which SAIL is an acronym of keeping the prescribed regimen as *Simple* as possible, be *Aware* of the potential adverse effects, explore the *Indication* and *List* each medication on the list and hand it out to the patient. TIDE is also an acronym, which outlines the rellevance that scheduling *Time* during a visit to manage medications, to remember the prescriber the *Individual* response to medications, to avoid potential *Drug-to-drug* interactions and *Education* of the patient.

Brown bag approach is another strategy, in which an older patient presents to the practice and hands the physician a bag with several medications. Thus, the prescriber must sort it out and prioritze among these medications [47].

Prescribing audits, such as Self-audit tool in *ECAP* clinical data station in Catalonia, feedback procedures, educational interventions to prescribers or patient education are other strategies.

However, it is worth mentioning that scientific literature has not found solid evidence that interventions using validated measures of inappropriate prescribing, for instance MAI, STOPP/START or Beers, improve the appropriate use of polypharmacy for elderly [16]. 2018 Cochrane systematic review, which included 32 high-quality studies, describes as "uncertain" a) whether pharmaceutical care improves medication appropriateness (measured by an implicit tool), b) whether pharmaceutical care decreases the number of potentially inappropriate medications and c) pharmaceutical care makes little or no difference in hospital admissions. Furthermore, this review casts serious doubts on the slight reduction of the number of PPO and qualifies it as uncertain, too.

3.4 DEPRESCRIPTION IN OUR PRIMARY HEALTH CARE SETTING.

The access to primary healthcare in Catalonia is guaranteed by the CATALAN HEALTH SERVICE (*Servei Català de Salut* - CatSalut), which acts as a public health insurer to all the citizens and it is responsible for the hiring of suppliers for this service. In our region, the biggest healthcare supplier is the CATALAN INSTITUTE OF HEALTH (*Institut Català de la Salut* - ICS), which manages 27 primary health teams (PHT) in Girona health region, as well as Girona's tertiary referral hospital. Thus, ICS has 34 Primary healthcare centres, as well as 115 local clinics, which are integrated into the COMPREHENSIVE PUBLIC HEALTH SYSTEM OF CATALONIA (*Sistema sanitari integral d'utilització pública de Catalunya* - SISCAT) and they attend an approximate population of 838.103 people, only in Girona health region [48].

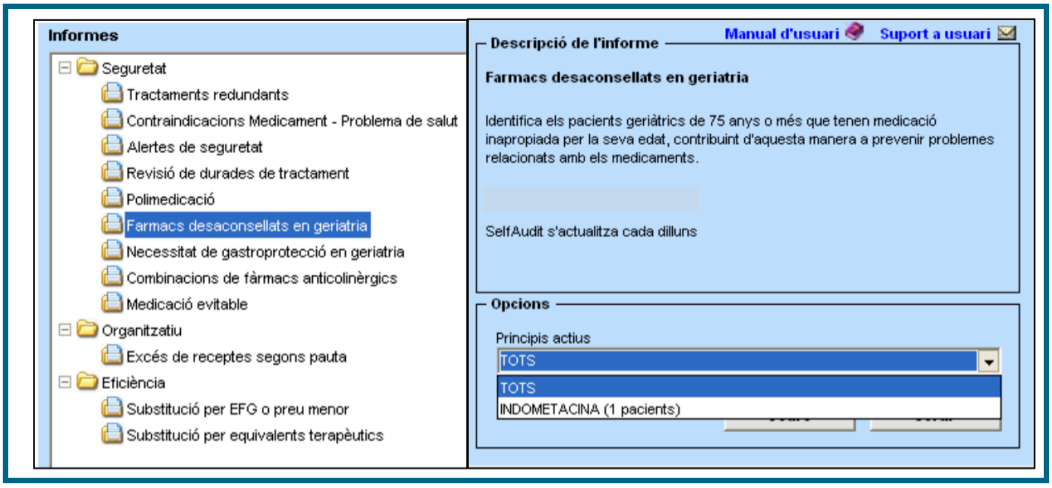
ECAP [49] is a computer-based clinical history, which is used by family medicine physicians, paediatricians and nurses in the vast majority of Catalan primary attention healthcare centres when they visit their patients. It offers not only an integral vision of the patient and its health status, but also it is a decision-making tool. Within its many features, it helps to manage prescribed medications in their assigned patients: pharmacological duplicities, contraindications for a specific condition, inadequate duration of a treatment, not advisable

medication due to age, contraindications due to AEMPS[2] security alerts, drug combinations that entail a potential risk, among others. Thus, it also facilitates the change and the stoppage, if necessary, of medication in a fast and effective manner.

Furthermore, it also promotes efficiency, since it detects those patients taking a medication which could be changed by a therapeutic equivalent drug. All in all, more than 500.000 incidences related to medication are solved thanks to this tool.

Several aspects related to medication revision are carried out on the basis of a voluntary self-analysis with the help of an integrated complementary tool in ECAP called Self-audit.

SELF-AUDIT is able to help with the management of geriatric patients with inappropriate medication due to his/her age, therefore contributing to avoid medication-related problems [50]. Thus, the healthcare provider is able to request a report to this tool, which shows the list of patients aged above 75 years old who have any of the 72 active ingredients selected as potentially inappropriate in his/her active prescription [>>ANNEX 2]. These 72 active ingredients are selected according to Beers, STOPP-START, PRISCUS and EU-PIM criteria and those which may be included in more than 2 bibliographic databases, with a specific alert by the AEMPS, with an explicit recommendation or contraindication on aged population in its datasheet or with the consensus of an expert group. The programme, then, offers an alternative or advice to the healthcare provider in order to facilitate the selection of a pharmacological treatment on aged people, taking into consideration that each patient has its own features and treatment must be individualized.



>> IMAGE 1. Self audit tool screenshot in ECAP. Source: own elaboration.

However, in spite of the help that ECAP and SelfAudit entail, nowadays there is not an implemented tool that helps primary care healthcare providers to identify those patients taking ASA as primary prevention and advise them against its use.

Polymedication in our setting not a foreign problem. Although we have not been able to check other Catalan regions' data, we indeed were able to check Girona's one[3].
According to ECAP data, in October 2020, 72.325 medication packagings had been dispensed to 29.054 people older than 65 years who took 5 or more ATC in that same month, in other words, these above-mentioned number of people had taken 9,37 medication packages per person.
If we take into consideration, those patients above 65 years old who took more than 15 medications in Girona health region during that very same period, we can check a rate of 1,63 per 1000 inhabitants, being especially higher in Marítim PHTs[4] with a rate of 2,55 per 1000 inhabitants.

Nonetheless, if we take into account only those patients above 65 years old who took between 10 and 14 medications, the number increases considerably: 97.262 took them, in other words, 15,81 per 1000 inhabitants. Again, Marítim PHTs have the highest rate of polimedication in these group of population per 1000 inhabitants (20,72 per 1000).

As a matter of fact, the 2016-2020 Health Plan for Catalonia [51] elaborated by the Catalan Health Ministry includes in its project 5.2 and 5.4 several working themes set for 2020 that are directly related to polypharmacy, deprescription and optimization strategies such as "*Develop optimization politics and efficient selection of the medicine*", "*To establish a model for the revision of treatments for chronic and polymedicated patients and to introduce tools for the improvement of balance in prescription, distribution and compliance of treatments*" or "*To establish actuation plans for the detection of clinical security problems related to medicines, so as to implement follow-up of safe usage of medicine lines and estimation of impact on potential users*".

[3] Girona Catalan Institute of Health primary health teams (Equips d'Atenció Primària de l'ICS Girona) data

[4] Blanes, Canet de Mar, Pineda de Mar, Sant Feliu de Guíxols and Tordera PHTs

When it comes to the Girona health area, the strategic plan for Girona health area 2017-2020 [52] highlights in its objective 1.4, the need to carry on making progress on the improvement strategy on the attention of the complex chronic patient (CCP) and advanced chronic ill patients (ACIP). Both CCP and ACIP groups of patients tend to be polymedicated and subject to more ADE, as stated above.

3.5 ACETYLSALYCILIC ACID AND ITS CURRENT USE.

> ACETYLSALYCILIC ACID.

ASA is one the most used medicines in the world. Its precursor is extracted from the bark of the willow tree and from many centuries ago, its analgesic and antipyretic properties have been known by Egyptians and Sumerians [53]. As a matter of fact, it is thanks to the discovery of several ancient Egyptian documents, in which the use of willow for the relief of non-specific pains is described, that further research on this field was carried out.
Although the discovery of ASA is a disputed fact, Arthur Eichengrün, head of the pharmaceutical division of Bayer, Felix Hoffmann, a chemist, and Heinrich Dreser contributed to it. In 1897, pure ASA was synthesized, combining salicylic acid with acetic acid. Thus, the nauseous effect of pure salicylic acid was removed.
In 1950, Lawrence Craven proved the cardiovascular benefit that implied its use in MI prevention, while later on, in 1956, its effects on the prevention of ischemic strokes was noted. In the 1960s, John Vane described for the first time its mechanism of action, that is, the inhibition of the synthesis of prostaglandins. For this reason, he won the Nobel Prize for Physiology or Medicine in 1982.

> ASA AND ITS ANTIPLATELET ACTIVITY.

Prostaglandins (PG) are lipid-soluble molecules synthesized from arachidonic acid by cyclooxygenase (COX). There are 2 main isoforms: COX-1 and COX-2.
COX-1 is present in all tissues, it is the constitutive form of the enzyme, and is involved in platelet aggregation through production of thromboxanes (TX), whilst COX-2 is expressed in inflammatory responses and is involved in upregulation of PG, which have vasodilator and anti-aggregatory actions. COX-1 and COX-2 are involved in protection of the gastric mucosa. In experimental settings, low doses of ASA inhibits COX-1 and disrupts the synthesis of TXA2, reducing platelet aggregation and formation of a thrombus. Higher doses of ASA

inhibit COX-2, leading to reduced production of prostacyclin and PGE, which entail analgesic and antipyretic effects, but also can promote vasoconstriction, renal dysfunction, hyponatremia and proaggregatory effects.
Thus, arachidonic acid is the substrate to form prostaglandin H2, which can be converted to thromboxane A2, prostacyclin or other types of prostaglandins [54].

ASA acetylates COX-1 and COX-2 irreversibly, preventing the access of arachidonic acid to the catalytic active of the enzyme, hence preventing further synthesis of TX.
TX induces platelet aggregation and acts as a vasoconstrictor and a smooth cell mitogen.
ASA also blocks the synthesis of PG, especially prostacyclin. In fact, both prostacyclin and TX are in a homeostatic balance, since they have opposite effects on platelet aggregation [55].
This antiplatelet effect of ASA is especially used in SECONDARY PREVENTION. In other words, it is prescribed to patients with increased cardiovascular risk, usually >20% over 10 years. However, ASA increases the probability of bleeding (eg. gastrointestinal, intracranial hemorrhage).
ASA is also used as prophylaxis of several conditions (MI, ischaemic stroke, angina pectoris), as prevention of complications after surgeries (revascularisation, prosthetic heart valves) and as a treatment of several conditions such as ischaemic bone necrosis, TIA, antiphospholipid syndrome, MI or ischaemic stroke, among others.

> PRIMARY PREVENTION: THE EFFICACY OF ASA.

Whilst beneficial effects of ASA as secondary prevention have been widely proven, primary prevention beneficial effects have not.
Between 1988 and 2005, 6 clinical trials have been conducted which seemed to conclude that risk-benefit balance of ASA was positive. Then, antiplatelet therapy as primary prevention was regarded as beneficial [56].
However, from 2005 until nowadays, several studies have not found significant results in its primary endpoints (MI, non-fatal and fatal stroke, any atherosclerotic event, non-fatal and fatal coronary event, cardiovascular death) that cast several doubts on the efficacy of it.

In 2018, 3 studies changed the vision of the relationship between ASA and primary prevention. [>> TABLE 2] summarizes these trials.

>> ARRIVE TRIAL.

Use of Aspirin to Reduce Risk of Initial Vascular Events in patients at moderate risk of cardiovascular disease (ARRIVE) trial studied a population of 12.546 individuals with a moderate cardiovascular risk, that is between a 10-20% estimated 10-years risk of coronary heart disease, who were given ASA 100 mg vs placebo. [57] The sample was characterized by counting with 29% of smokers, 63% of hypertense, 58% of patients with hyperlipidaemia and no patients with diabetes mellitus.

ASA showed no reduction in major cardiovascular events (269 ASA vs 281 placebo, HR 0,96 95% CI 0,81-1,13, p=0,60) or all-cause mortality (ASA 160 vs placebo 161, HR 0,99, CI 95% 0,8-1,25, p=0,95), whilst gastrointestinal bleeding events were 2 times higher in ASA group (61 ASA, 29 placebo, HR 2,11, 95% CI 1,36-3,28, p=0,0007)

Cardiovascular risk score in this group was 17,3% and event rates of cardiovascular risk were lower than expected (<10% in 10 years). Thus, some authors claim [56] that this study is underpowered. Furthermore, almost half of the participants were on statin therapy and almost two-thirds of them received anti-hypertensive treatment, too, proving, at the same, the benefits of current cardiovascular disease preventive treatment.

>> ASA, PRIMARY PREVENTION & DIABETES MELLITUS.

The Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus (ASCEND) was published in 2018 and took a sample of 15.480 people over 40 years and with DM and no cardiovascular disease with ASA 100 mg daily or placebo. [58] The primary endpoint, that is a composite of MI, stroke, cardiovascular death, UA and TIA, took place in 658 (8,5%) on ASA vs 743 (9,6%) on placebo, (rate ratio 0,88, 95% CI 0,79-0,97, p=0,01). Thus, severe cardiovascular events took place in a lower proportion of ASA group. However, it was at the expense of a significant increase in major bleeding in the ASA group: 314 (4,1%) patients on ASA vs 245 (3,2%) on placebo (rate ratio 1,29, 95% CI 1,09-1,52, p= 0,003).

Thus, NNT was 91 and NNH 112.

No differences were appreciated in all-cause mortality (748 vs 792, rate ratio 0,94, 95% CI 0,85-1,04), in non-fatal MI (191 vs 195, rate ratio 0,98, 95% CI 0,8-1,19) or in stroke (202 vs 229, rate ratio 0,88, 95% CI 0,73-1,06).

The sample of this study has more men (63%), a high BMI (mean: 30,7; BMI >25, 85%) and there were few smokers (8%). The majority of the participants received statin-based therapy, as well as anti-hypertensive treatment.
As a matter of fact, during the trial, TIA was added as a primary endpoint, sample was extended as well as duration of the study.

>> ASA, PRIMARY PREVENTION & ELDERLY.

ASPirin in Reducing Events in the Elderly (ASPREE) trial took a sample of 19.114 people, who were over 70 years old, were healthy (they had not dementia, disability or cardiovascular diseases) and had a >10% risk of cardiovascular risk [59, 60, 61]. After a follow-up of almost 5 years, ASA did not decrease the rate of death, dementia or persistent physical disability (21,5 ASA vs 21,2 placebo per 1000 person-year, HR 1,01, 95% CI 0,92-1,11, p=0,79) and increased the haemorrhage episodes (8,6 ASA vs 6,2 placebo per 1000 person-year, HR 1,38, 95% CI 1,18-1,62, p<0,001). Furthermore, all-cause mortality turned out to be higher in ASA group (12,7 ASA vs 11,1 placebo per 1000 person-year, HR 1,14, 95% CI 1,01-1,29), which was attributed to excess cancer mortality.

> META-ANALYSIS.

Mahmood et al 2019 meta-analysis [62] took 11 primary prevention ASA trials, with 157.248 participants, which found no reduction in all-cause mortality. Furthermore, a 0,6% increase in absolute risk of major haemorrhage and 0,1% increase in intracranial bleeding was found. A reduction in MI is found in pre 2000 years studies (0,82, 95% CI 0,71-0,94, p=0,006), however, if we take post 2000 trials, the difference is not significant (0,90,0,79-1,02, p=0,10)
Zheng et al revised 13 trials [63] from 164.225 participants and they checked that ASA reduced the composite outcome of cardiovascular mortality, non-fatal MI and non-fatal stroke (HR 0,89, 95% CI 0,84-0,95) with an absolute reduction of 0,38 and a NNT=265. There was no difference in all-cause or cardiovascular mortality and there was an increase of major haemorrhage events (HR 1,43, 95% CI, 1,30-1,56) with an absolute risk increase of 0,47%, NNH= 210.
Recent trials showed even less benefit, since they did not prove a reduction in MI and the reduction in composite of cardiovascular outcome was poor (0,90, 0,83-0,98).

>> TABLE XXX: **RECENT RANDOMISED CONTROLLED TRIALS FOR ASA IN PRIMARY CARDIOVASCULAR PREVENTION**			
Name of the study *(acronym)*	**ARRIVE**	**ASCEND**	**ASPREE**
Publication year	2018	2018	2018
Enrolment period	2007-16	2005-11	2010-14
Sample size	12.546	15.480	19.114
Population	Men over 55 years with 2-4 cardiovascular risk factors. Women over 60 yrs with 3 or more cardiovascular risk factors.	Men and women over 40 years with diabetes mellitus.	Men and women over 70 years.
Control group	Placebo	Placebo	Placebo
Follow-up (years)	Median 5	Median 7,4	Median 4,7
Participant age (years)	Mean 64	Mean 63	Mean 74
Smokers (%)	29%	8%	4%
HTA	Mean systolic blood pressure 145, HTA 63%	Mean systolic blood pressure 136	Mean 139/77, HTA 75%
Hyperlipidaemia	Hyperlipidaemia 58%	Mean cholesterol: 4,2 mmol//L	Mean cholesterol: 5,2 mmol/L, hyperlipidaemia 66%
Statin use (%)	43%	75%	34%
DM (%)	0%	100%	11%
Bodyweight	Mean BMI 28,4 BMI >25,79%	Mean BMI 30,7 BMI >25,85%	BMI > 30 30%
Women (%)	30%	37%	56%
Men (%)	70%	63%	44%
ASA dosage (mg)	100 mg	100 mg	100 mg

Primary endpoint (ASA vs control)	*Major cardiovascular events (composite of MI, stroke, cdv death, UA, TIA):* 269 ASA vs 281 placebo, HR 0,96, 95% CI 0,81-1,13, p = 0,60	*Major cardiovascular events (composite of MI, stroke, cdv death, UA, TIA):* 658 vs 743, OR 0,88, 95% CI 0,79-0,97, p=0,01	*Death, dementia or persistent physical disability* 21,5 vs 21,2 per 1000 person-year, HR 1,01, 95% CI 0,92-1,11, p=0,79
Secondary endpoints (ASA vs control)	*Composite of individuals outcomes of the time to cardiovascular death, myocardial infarction or stroke, time to unstable angina, time to TIA, and time to death.*	*Any major vascular event* 833 vs 936 RR 0,88 95% CI 0,8-0,97	*Major cardiovascular events:* 10,7 vs 11,3 per 1000 person-years HR 0,95, 95% CI 0,83-1,08
Safety endpoint (ASA vs control)	*Gastrointestinal bleeding events* 61 vs 29, HR 2,11, 95% CI, 1,36-3,28 p = 0,0007	*Major bleeding event* 314 vs 245 RR 1,29 95% CI 1,09-1,52, p=0,003	*Major haemorrhage* 8,6 vs 6,2 per 1000 persons-years HR 1,38 95% CI 1,18-1,62, p<0,001
All-cause mortality (ASA vs control)	160 vs 161 HR 0,99 CI 0,8-1,24, p = 0,95	748 vs 792 RR 0,94 95% CI 0,85-1,04	12,7 vs 11,1 per 1000 person-years HR 1,14 95% CI 1,01-1,29
Myocardial infarction (ASA vs control)	*Non fatal* 88 vs 98 HR 0,9 95% CI, 0,67-1,20, p=0,46	*Non-fatal* 191 vs 195 RR 0,98 95% CI 0,8-1,19	*Fatal or non-fatal* 171 vs 184 HR 0,93 95% CI 0,76-1,15
Stroke (ASA vs control)	*Fatal or non fatal* 75 vs 67 HR 1,12 95% CI 0,8-1,55, p= 0,51	*Non-fatal* 202 vs 229 Rate ratio 0,88 95% CI 0,73-1,06	*Fatal or non-fatal* 148 vs 167 HR 0,89 95% CI, 0,71-1,11
Source: Adapted from Raber et al [59]			

> INTERNATIONAL GUIDELINES.

>> EUROPEAN SOCIETY OF CARDIOLOGY (ESC) 2016.

European Guidelines on cardiovascular disease prevention in clinical practice [64] do not recommend antiplatelet therapy in individuals without cardiovascular risk, due to major haemorrhage, with a class of recommendation A and a level of evidence B. The recommendation is based on studies such as Antithrombotic Trialists' Collaboration, which found a risk reduction from 0,57% to 0,51% year of serious vascular events combined with a major gastrointestinal and extracranial haemorrhage increased or Japanese Primary Prevention Project (JPPP), which also confirmed the higher risk of serious haemorrhage when given ASA to patients above 60 years with hypertension, dyslipidemia or DM. Thus, this guideline was published before the 3 above-mentioned 2018 studies had been published.

>>AMERICAN HEART ASSOCIATION (AHA) 2019.

ACC/AHA Guideline on the Primary Prevention of Cardiovascular disease [65] mentions that, whilst ASA is widely proven for secondary prevention, primary prevention is still controversial.

The guideline considers that administration of low-dose ASA (75-100 mg orally daily) both for adults > 70 years of age and any adult with increased risk of bleeding as primary prevention should not be given. Both recommendations are classified with a level 3, that is, there is more risk than benefit, however the level of evidence differs according to it. Whilst the first recommendation has a level of evidence B-R (moderate-quality evidence from 1 or more RCT or meta-analyses of moderate-quality RCTs), the second has a level C (limited data).

However, the same guideline considers that low-dose ASA may be considered for primary prevention of atherosclerotic cardiovascular disease among adults between 40-70 years who have higher ASCVD risk, but do not have an increased bleeding risk. This piece of advice is classified with a level 2b and a level of evidence type A.

Prophylactic use of ASA as primary prevention in those aged over 70 years is potentially harmful, plus, there is often an increased risk of haemorrhage. Thus, it is difficult to justify its use, according to the guideline.

In adults below 40 years, the same guideline says that there is not enough evidence to value the risk-benefit of routine ASA as primary prevention of ASCVD.
Nonetheless, they stress that there in some selected situations with other associated risk factors (strong family history of premature MI, inability to reach target glucose, lipid or BP level, high coronary artery calcium score) there is still not enough evidence.
They also recommend to avoid prophylaxis when there are haemorrhage risk factors such as previous gastrointestinal haemorrhage, peptic ulcer, thrombocytopenia, age above 70, coagulopathy, chronic kidney disease and use of medications which increase bleeding risk.

>> AMERICAN DIABETES ASSOCIATION (ADA)

Whilst ADA [66] guidelines do recommend ASA therapy as a secondary prevention in those with diabetes and a history of atherosclerotic cardiovascular disease, ASA as primary prevention is only considered for those with diabetes and high cardiovascular risk, after having discussed with the patients the risk and benefits.
Thus, they recommend ASA as primary prevention for those aged over 50 years with diabetes and at least one additional major risk factor (HTA, dyslipidemia, smoking, CKD/albuminuria, family history of premature ASCVD) who are not at higher risk of haemorrhage (anemia, renal disease, older age). The guideline also indicates that patients over 70 years old with or without diabetes seem to have more risk than benefit and might not be recommended. Patients with high cardiovascular risk and low haemorrhage risk may be considered for treatment, but never in older patients.

> ASA SITUATION IN OUR SETTING.

Although specific medication information is unavailable, we could check information regarding ATC B01AC *Platelet aggregation inhibitors excluding heparin*, where ASA is included. The following table summaries the evolution of this prescription from 2017 to 2019 throughout Catalonia [67]:

>> TABLE 3: **ANTIPLATELET AGENTS EXCLUDING HEPARIN USE IN CATALONIA.**

	2017			2018			2019		
Age range (years)	65-74	75-84	> 85	65-74	75-84	> 85	65-74	75-84	> 85
Number of dispensed packagings	1.307.777	1.358.226	882.665	1.255.960	1.285.561	845.739	1.266.555	1.306.563	876.767
Assumed expenses by CatSalut (EUROS)	5.519.856,75	5.657.929,2	3.571.526,22	5.548.439,30	5.447.130,56	3.485.283,09	5.489.207,01	5.412.906,63	3.471.353,95

DATA SOURCE: Own elaboration, data from **Pharmaceutical Provision Unit, Servei Català de la Salut,** based on *Llei 19/2014 de transparència, accés a la informació i bon govern*

Regarding Girona health region, from January to October 2020, ASA was the fourth most dispensed medication among patients above 65 years old in Girona Catalan Institute of Health primary healthcare teams [>>ANNEX 3] according to ECAP.
However, when the top fifteen medication which entail more costs for our health system were considered, ASA did not appear, probably due to the low cost of it [>>ANNEX 4].

4. JUSTIFICATION

Taking into consideration all these previously-mentioned information, we can claim that polimedication is present among older population in Girona health region and that ASA is one of the commonest medications used in our environment. Despite the fact that our health care system has already active strategies so as to deal with polypharmacy, such as *Self-audit* in ECAP, and even a national health plan that outlines the importance of coping with it, it may seem as though other strategies could be implemented so as to manage synergically this issue, taking into account the statistics of the problem.

Furthermore, we can assert that ASA in older population for primary prevention seems not to be appropriate owing to its risks and lack of efficacy..

Not only it increases risk of bleeding events but also it has limited efficacy in preventing cardiovascular events and mortality. Updated guidelines recommendations recommend against initiating ASA for primary prevention in older people. Meta-analysis, such as *Mahmood et al* and *Zheng et al* ones, are also sided with the idea that ASA for primary prevention is inadequate.

Nevertheless, we are not able to attribute all those unjustified ASA prescriptions to the fact that they are potentially inappropriate prescribed. Maybe there are patients who are taking ASA and should continue doing so because an appropriate diagnosis is not well-labelled in their clinical record.

Therefore, under this assumption and taking into account the serious doubts casted by interventions using different implicit and explicit deprescription criteria, our doubt is whether a certain intervention centered on unjustified ASA prescription and focusing a determinate segment of population will make healthcare providers at a primary healthcare level improve ASA prescription appropriateness, which would imply an improvement of its own indication.

5. OBJECTIVES

The primary objective of the present study is to guarantee ASA prescription quality in a determinate primary health care setting and within a definite range of age, those with 65 years and older, by implementing a structured educational intervention.

According to EPOC Taxonomy [68], our intervention could be classified as an Implementation Strategy, defined as a strategy which aims to bring about changes in healthcare organization, the behaviour of healthcare professionals or the use of health services by healthcare recipients, and could be subcategorized as a Continuous Quality Improvement. The latter subcategory is defined as an iterative process to review and improve care that includes involvement of healthcare teams, analysis of a process or system, a structured process improvement method or problem solving approach, and use of data analysis to assess changes.

The secondary objectives of the trial are the following ones:

- To assess whether the potential ASA inadequacy prescription change is due to the fact that it is not well-prescribed and it is, therefore, a PPI or it is owing to the fact that it has not been correctly labelled in the clinical history.
- To evaluate which is the covariate (BHA area type and socioeconomic status[5]) that influences the most in guaranteeing ASA prescription quality.

Our hypothesis is that the implementation of a short, defined, simple and groupal intervention, as ours, will help to improve ASA prescription quality.

[5] BHA area type and socioeconomic status are defined in page 38

6. METHODS

We designed a community intervention trial following 2010 Consolidated Standards of Reporting Trials (CONSORT) guidelines [69], which aim to report cluster randomised trials in an accurate and transparent way. Approval by IDIAP Jordi Gol clinical ethics committee is still pending.

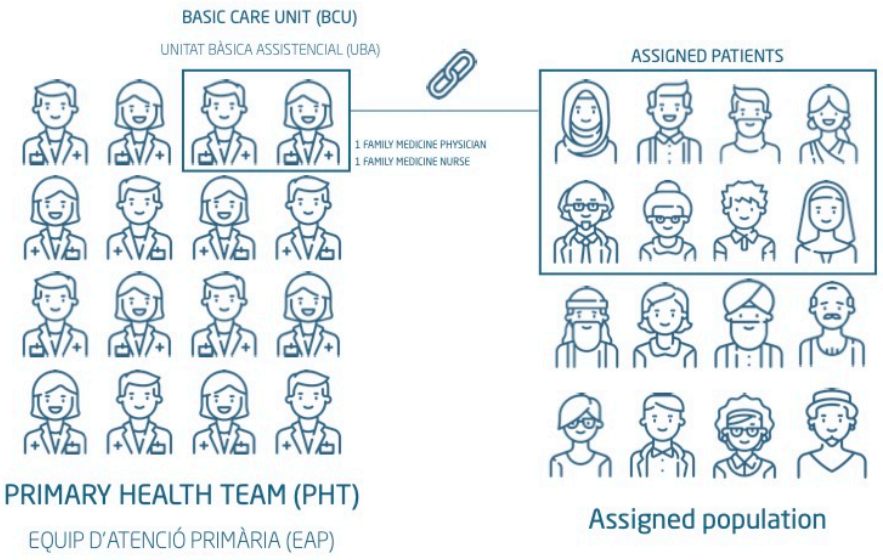
6.1 TRIAL DESIGN.

This study is intended to be a COMMUNITY INTERVENTION TRIAL with a one-year and 3 months follow-up and POPULATION-BASED, in which an educational intervention on ASA quality prescription in 65 years individuals and older on family medicine physicians and nurses is assessed.

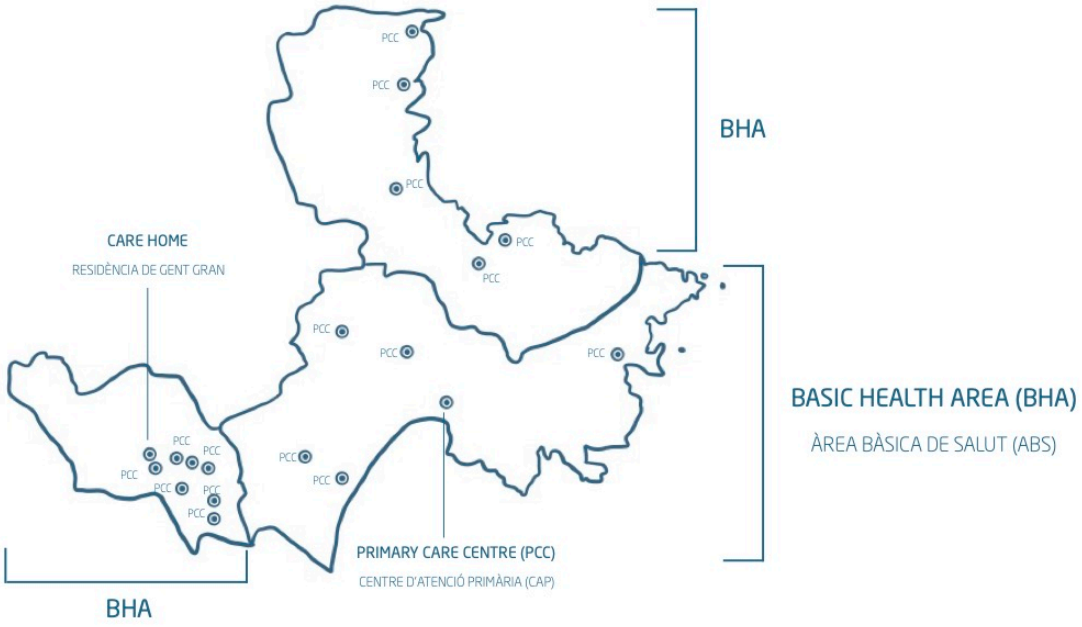
6.2 PARTICIPANTS.

> ELIGIBILITY CRITERIA FOR CLUSTERS.

The eligibility criteria for clusters of our study are those Primary healthcare teams (PHT), which work within a Basic health area (BHA) and belong to the Catalan Institute of Health (ICS). PHTs are formed by Basic care units (BCU), which are made up of one Family Medicine physician and nurse who share a common list of assigned patients. BCUs may either work in a Primary care centre (PCC) or in a care home.



>> IMAGE 2. Structure of primary health teams. Source: own elaboration and www.flaticon.com



>> IMAGE 3. Structure of basic health areas. Source: own elaboration.

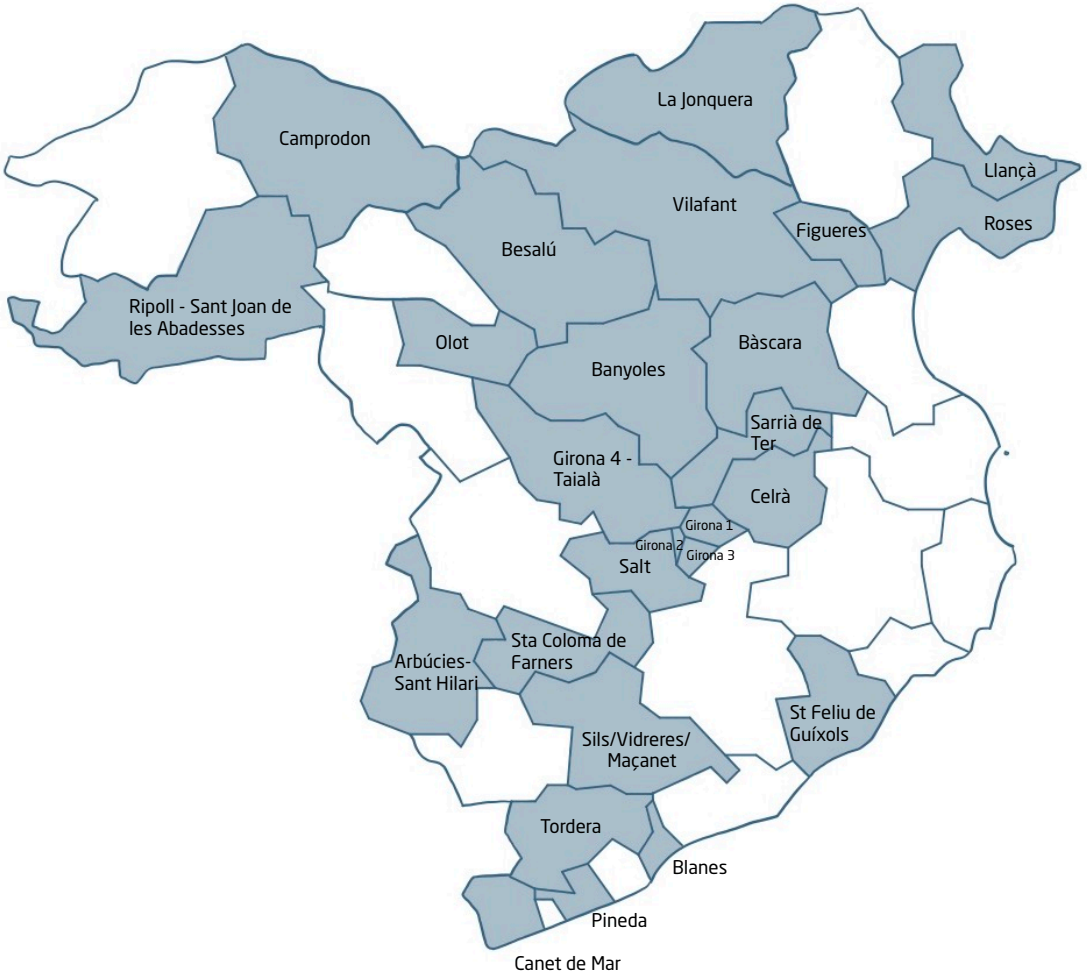
Thus, we will be including the following 26 PHTs into our study, which attend 584.619 people: Arbúcies-Sant Hilari Sacalm, Banyoles, Bàscara, Besalú, Blanes, Camprodon, Girona 2 - Can Gibert del Pla, Canet de Mar, Celrà, Figueres, La Jonquera, Llançà, Girona 3 - Montilivi/Vila-roja, Olot, Pineda de Mar, Ripoll, Roses, Salt, Sant Feliu de Guíxols, Girona 1 - Santa Clara, Santa Coloma de Farners, Sarrià de Ter, Sils-Vidreres-Maçanet de la Selva, Girona 4 - Taialà, Tordera and Vilafant.

We will be excluding Penitentiary Figueres PHT due to its particular population and features. All in all, our study will be, by including these PHTs, taking into account nearly 70% of all the PHTs assigned population in the whole Girona health region.

> DATA SOURCE.

Data will be provided by SIDIAP (Catalan Information System for the Development of Research in Primary Care - *Sistema d'informació pel Desenvolupament de la Investigacióa l'Atenció Primària*), which contains anonymous longitudinal patient information, including medications prescriptions. SIDIAP includes all the available clinical information from the general population.

The quality of SIDIAP data is already proven and it has been widely used in several studies [70, 71]. The current data appearing on this protocol have been extracted from ECAP clinical data station by the Technical Secretary and Clinical Development Area of Territorial Management of the Catalan Institute of Health in Girona.



>> IMAGE 4. Included primary health teams in the study within Girona health region. Source: own elaboration.

6.3 INTERVENTIONS.

We will be forming two different groups:

> INTERVENTION GROUP.

Group of PHTs who will have received an educational intervention on ASA quality in 65 years and older population. The educational intervention will consist of the following steps:

>> TEAM SESSION *for* INTERVENTION PHTs *on* ASA QUALITY *in 65* YEARS *and* OLDER POPULATION PRESCRIPTION.

- Sessions will be online, due to the current COVID-19 pandemic. Although each PHT has already a programmed session in the calendar [>>TABLE 9], these may be subject to change according to their specific schedule and each PHT direction will be responsible to announce it and arrange it.
- 3 live sessions will be delivered throughout the period of 1 year and 3 months. Each of them will have an estimate duration between 45 and 60 minutes and they will have a separation time of 3 months between each of them. The first part of the session will be based on cases presentation on ASA prescription and it is intended to have a practical focus. This part will have a duration of 30 minutes, whilst the second part, 30 minutes, in which participants will be able to express their questions and doubts. This presentation is still provisional and it is subject to change according to the pilot study result. [>>ANNEX 5] Sessions programmed for PHTs with a few number of professionals may be broadcasted for more than one PHT. Thus, Llançà and Vilafant PHT, Camprodon PHT and La Jonquera PHT, Besalú and Santa Coloma PHT and Bàscara PHT and Tordera PHT will have joined sessions.
- Once the session is over, the recording of it will be sent to the PHT direction so that health care providers may watch it later. Furthermore, a practical brief summary leaflet of the session [>>ANNEX 6] will be delivered, where the main indications and codes of ASA prescription will be written down.
- Due to the fact that in every PHT there is a clinical referent, healthcare providers with doubts on the topic will be able to consult him/her.
- PHT clinical referents already have an assigned pharmacology expert with whom they will be able to contact to refer their doubt on the topic.

- Regular feedback on ASA quality will be sent monthly automatically to each intervention PHT direction by ICS Girona regional management office approval (*Gerència Territorial de l'Institut Català de la Salut a Girona*).
- Educational booster sessions will have a similar format to the first educational session but with a different content. According to the specific doubts and problems derived from the intervention, clinical cases will be readapted and created. Hence, we plan that the content of these sessions are adapted to the necessities of the PHTs and are not static.

>> PATIENT INFORMATION LEAFLETS.

- A brief and basic summary on ASA indications has been included and it is planned to be handed out to those patients who will have an adjustment of ASA quality prescription [>>ANNEX 7].
  - According to 2019 data, nearly a 20% of Girona region population comes from abroad. Despite the mean age of resident foreigners is relatively young (35,34 years), we will guarantee that leaflets are available in frequently spoken languages by this segment of population, such as English, French, Romanian, Punjabi, Arabic and Mandinka [72].

- Both professionals and patients leaflets have been based on Tasmania's primary health ones. [73, 74] Researchers contacted with the leaflets' authors and obtained consent for their modification. This consent can be found in [>>ANNEX 13].

> CONTROL GROUP.

Group of PHTs who will not have received an educational intervention on unjustified ASA prescription.

ICS Girona regional management office (*Gerència Territorial de l'Institut Català de la Salut a Girona*) will be informed of the study execution, they will only know that there are PHT selected as *Intervention* and *Control*. Thus, they will inform all PHT directions that this study will be carried out, without letting know the allocation of both groups.

Hence, those PHT which are randomly selected as Intervention will be contacted through the PHT direction mail. This person is intended to be the only person in the whole PHT that knows this piece of information.

> CATALAN CONTEMPORANEOUS COMPARISON GROUP.

Since we predict that control group behaviour may be altered by Hawthorne effect, we will be analysing anonymised data of all Catalan PHTs, which can be obtained through SIDIAP database, as a national contemporaneous comparison group. We will request data on percentage of 65 years and older patients who are taking unjustified ASA prescription, according to our criteria, before the intervention and monthly, during the intervention. Thus, we will be able to assess the ecological evolution of the problem in our environment and the tendency in it.

> PILOT STUDY.

Before carrying out this trial, we will be performing a pilot intervention taking as a reference Medical Research Council (MRC) framework on the development and evaluation of complex interventions [75]. This framework is used to improve the development, evaluation and implementation process of a complex intervention. Thus, it will help us to check whether our intervention is feasible or may be needed to be modified before carrying out this trial.
As a matter of fact, within all the studies included in the 2018 Cochrane systematic review , only one study referred using these MRC guidelines [12].
For this purpose, since the main researchers of this study are integrated within Girona 3 - Montilivi/Vila-roja PHT, we will execute the pilot study within this team, since it will be easier to carry it out and due to the fact that the PHT has enough assigned patients so as to draw conclusions from this pilot study and allow us to make changes in this intervention.

6.4 OUTCOMES.

PRIMARY VARIABLE:

- Percentage of 65 years and older patients who are taking unjustified ASA, according to our criteria, in intervention and control clusters.

SECONDARY VARIABLE:

- Improvement of register of ASA intake & linked to its indication in intervention and control clusters.
- Percentage of polymedicated patients, that is intake of 5 or more medications, within a BHA in intervention and control clusters.

INDEPENDENT VARIABLE (EXPOSURE):

Implementation of a structured intervention: It is a qualitative dichotomous variable (Yes/No).

DEPENDENT VARIABLE (OUTCOME):

Reduction of prescribed ASA. It is a continuous quantitative variable (%, percentage of unjustified prescribed ASA).

COVARIATES:

There are other variables that may affect our independent and dependent variables, but they are not the aim of this study. These variables may act as confounders, thus, we will have to control them so that our study has more external and internal validity.

- Basic health area type: it is a qualitative dichotomous variable (rural or urban).
- Socioeconomic level: Average income per person (*in Euros*). Since it is a quantitative continuous variable, but does not follow a normal distribution, we will organise it by terciles. This measure is calculated as the average of the years 2015, 2016 and 2017. The variable is observed at a census track level [76].

6.5 SAMPLE SIZE.

In order to calculate the need sample, we will be using a free online software (GRANMO) [77].

To respond to the primary objective of the study, and based on previous studies, estimating a clinical relevant difference of 50% between groups and assuming a 5% loss to follow-up, an inclusion of 2015 patients per group is estimated, 4030 patients in total.

We have taken into account an alpha error of 0,05 and a statistical power of 0,9.

SIZE:

The target population are all those above-mentioned PHT, which belong to the Catalan Institute of Health.

In order to determine the impact of the intervention in both groups, we will analyze the number of assigned patients in every participating PHT who are over 65 years old and are codified as taking ASA without a secondary prevention indication in their clinical record (ECAP). The following diagnosis could justify ASA use in these group of patients, according to *International Classification of Diseases, tenth revision, clinical modifications* (ICD-10-CM):

- D68.62: Lupus anticoagulant syndrome
- E10: Type 1 diabetes mellitus
- G45: Transient cerebral ischaemic attacks and related syndromes
- H34.10: Central retinal artery occlusion, unspecified eye
- I20-I25: Ischemic heart diseases
- I21.9: Acute myocardial infarction, unspecified
- I48: Atrial fibrillation and flutter
- I60-I69: Cerebrovascular diseases
- I70: Atherosclerosis
- I73.9: Peripheral vascular disease, unspecified
- I80.3: Phlebitis and thrombophlebitis of lower extremities, unspecified
- I80.9: Phlebitis and thrombophlebitis of unspecified site
- M32.9: Systemic lupus erythematosus, unspecified
- Z95.2: Presence of prosthetic heart valve
- Z.95.3: Presence of xenogenic heart valve

In the following link [>> ICD-10-CM specific diagnosis], there is a more complete and specificied list of these above-mentioned *ICD-10-CM* patients' diagnosis.

After having analyzed the requested number of patients with the previous conditions and without personal data, we have concluded that there are approximately 9085 patients in the above-mentioned assigned-PHT population taking unjustified ASA, that is a 6% of the whole health region population.

It is rellevant to mention that this list of diagnosis that could justify ASA intake could be modified and improved after pilot study.

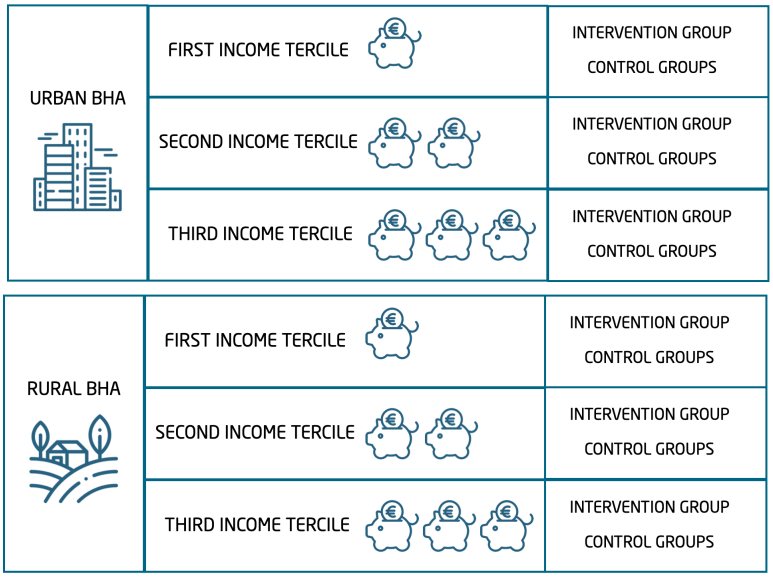
6.6 RANDOMIZATION.

In order that groups can be comparable, randomization will be done by BHA clusters according to two categories:

- BHA AREA TYPE.
- SOCIOECONOMIC STATUS.

Blocks will be defined according to the BHA type (urban or rural) and within each of these blocks, according to their socioeconomic status (income terciles). Once randomization has been carried out, we will assess whether the number of 65 years and older assigned patients is similar between groups.

We carried out this process with the help of a free, interactive, closed source, interactive and multi-module MS-DOS statistical software called Clinstat [78].



>>IMAGE 5. Diagram of cluster randomization. Source: own elaboration.

1. BASIC HEALTH AREA (BHA) TYPES.

BHA types may be classified according to whether they tend to be more rural or more urban. A dichotomous classification (rural/urban) is frequently used in our primary health context [79]. A municipality with more than 10.000 inhabitants and a population density greater than 150 inhabitants/km^2 was considered urban, whereas those with less than 2000 inhabitants were tagged as rural. Municipalities between 2000 and 10.000 inhabitants were regarded as intermediate. Thus, if all the municipalities of a BHA were considered rural, the BHA was

regarded as rural, whereas if all the municipalities of a BHA were considered urban, the BHA was tagged as urban.

If there was a discrepancy among municipalities, the BHA was considered urban if the sum of population of the localities within the BHA divided by 10.000 multiplied by the number of municipalities within the BHA was greater than 0,85 and if the BHA population density divided by 150 inhabitants/km^2 was greater than 0,85.

The following table shows the classification of BHA according to this criterion and annex 8 [>> ANNEX 8] shows the application of these above-mentioned criteria:

>> TABLE 4. CLASSIFICATION OF PHTs ACCORDING TO AREA TYPE

RURAL BHA	URBAN BHA
Arbúcies-Sant Hilari Sacalm	Blanes
Banyoles	Girona 2 - Can Gibert del Pla
Bàscara	Figueres
Besalú	Girona 3 - Montilivi/Vila-roja
Camprodon	Olot
Canet de Mar	Pineda de Mar
Celrà	Salt
La Jonquera	Sant Feliu de Guíxols
Llançà	Girona 1 - Santa Clara
Ripoll - Sant Joan de les Abadesses	Santa Coloma de Farners
Roses	Tordera
Sarrià de Ter	
Sils-Vidreres-Maçanet de la Selva	
Girona 4 - Taialà	
Vilafant	

DATA SOURCE: **Own elaboration.**

2. SOCIOECONOMIC STATUS.

Socioeconomic status may be measured through several indexes. We decided to use the average income per person (in Euros). Using the population of each of the census tract as weights, we calculated the weighted average of the values at the census tracts that composed the BHA to obtain their BHA level [>> ANNEX 9].

We decided to consider Girona 3 - Montilivi/Vila-roja PHT as intervention cluster in urban and third income tercile group since a pilot study will already be done and they will already

be more aware on the topic than other PHTs. Thus, we will try that our final result is not contaminated.

>> TABLE 5. CLASSIFICATION OF PHTs ACCORDING TO SOCIOECONOMIC STATUS

FIRST INCOME TERCILE	SECOND INCOME TERCILE	THIRD INCOME TERCILE
Figueres	Arbúcies/Sant Hilari	Besalú
Roses	Salt	Banyoles
Tordera	Girona 2 - Can Gibert del Pla	Celrà
Pineda de Mar	Canet de Mar	Olot
Blanes	La Jonquera	Sarrià de Ter
Sils/Vidreres/Maçanet de la Selva	Santa Coloma de Farners	Camprodon
Sant Feliu de Guíxols	Bàscara	Ripoll - Sant Joan de les Abadesses
Llançà	Girona 4 - Taialà	Girona 3 - Montilivi/Vila-roja
		Girona 1 - Santa Clara

DATA SOURCE: [70]

>> TABLE 6. FINAL BLOCKS ACCORDING TO BASIC HEALTH AREA TYPE AND SOCIOECONOMIC LEVEL.

URBAN FIRST INCOME TERCILE	URBAN SECOND INCOME TERCILE	URBAN THIRD INCOME TERCILE
Blanes	Girona 2 - Can Gibert del Pla	Girona 1 - Santa Clara
Figueres	Santa Coloma de Farners	Girona 3 - Montilivi/Vila-roja
Sant Feliu de Guíxols	Salt	Olot
Pineda de Mar		
Tordera		
RURAL FIRST INCOME TERCILE	**RURAL SECOND INCOME TERCILE**	**RURAL THIRD INCOME TERCILE**
Llançà	Arbúcies - Sant Hilari	Banyoles
Roses	Bàscara	Besalú
Sils/Vidreres/Maçanet de la Selva	Canet de Mar	Camprodon
	Girona 4 - Taialà	Celrà
	La Jonquera	Ripoll - Sant Joan de les Abadesses
	Vilafant	Sarrià de Ter

DATA SOURCE: Own elaboration.

By randomizing PHTs into an intervention and control group, we obtained the following results:

>> TABLE 7. **FINAL RANDOMIZED BLOCKS.**

	URBAN FIRST INCOME TERCILE	URBAN SECOND INCOME TERCILE	URBAN THIRD INCOME TERCILE
INTERVENTION	Pineda de Mar Figueres Tordera	Santa Coloma de Farners Girona 2 - Can Gibert del Pla	Girona 3 - Montilivi/Vila-roja Girona 1 - Santa Clara
CONTROL	Blanes Sant Feliu de Guíxols	Salt	Olot
	RURAL FIRST INCOME TERCILE	**RURAL SECOND INCOME TERCILE**	**RURAL THIRD INCOME TERCILE**
INTERVENTION	Sils/Vidreres/Maçanet Llançà	Bàscara Vilafant La Jonquera	Besalú Camprodon Banyoles
CONTROL	Roses	Canet de Mar Girona 4 - Taialà Arbúcies - Sant Hilari	Ripoll- Sant Joan de les Abadesses Celrà Sarrià de Ter

DATA SOURCE: Own elaboration.

Once randomization had been executed, we wanted to check whether the 65 years and older population in both intervention & control groups were similar, since, PHT assigned population varies. It is rellevant to point out that number of physicians and nurses in a PHT is assigned according to the number of assigned patients.

As we can see in the table below, intervention and control PHTs will have a similar number of assigned 65 years and older population. Hence, we considered that we could continue our trial.

>> TABLE 8. COMPARATIVE BLOCKS ACCORDING TO NUMBER OF 65 AND OLDER POPULATION			
INTERVENTION PHTs		CONTROL PHTs	
PHT	65 YEARS AND OLDER POPULATION [NUMBER]	PHT	65 YEARS AND OLDER POPULATION [NUMBER]
Pineda de Mar	6265	Blanes	7265
Figueres	8230	Sant Feliu de Guíxols	7092
Tordera	3085	Salt	5798
Santa Coloma de Farners	2828	Olot	7888
Girona 2 - Can Gibert del Pla	4547	Roses	5922
Girona 3 - Montilivi/ Vila-roja	5082	Canet de Mar	4624
Girona 1 - Santa Clara	4064	Girona 4 - Taialà	2636
Sils-Vidreres-Maçanet de la Selva	3981	Arbúcies-Sant Hilari Sacalm	2500
Llançà	1654	Ripoll - Sant Joan de les Abadesses	3627
La Jonquera	1579	Celrà	1511
Bàscara	994	Sarrià de Ter	2448
Vilafant	2396		
Besalú	1278		
Camprodon	1034		
Banyoles	6093		
TOTAL NUMBER WITHIN INTERVENTION BLOCKS	53110	TOTAL NUMBER WITHIN CONTROL BLOCKS	51311
DATA SOURCE: Own elaboration.			

6.7 BLINDING.

Primary health team directions will not be blinded, since they will be informed of the purpose of the study and whether their PHT is an intervention or control group. Health care providers which take part in an intervention PHT will not be either blinded, since they will have received an educational intervention and, moreover, they will receive periodically a PHT-level feedback on ASA prescription. Naturally, we intend that they do not know exactly the aim of the study.

Since professionals that analyze data are the same main researchers, they will not be blinded either.

6.8 STATISTICAL METHODS.

Data will be analyzed by using GNU PSPP programme for statistical analysis, a free software [80].

DESCRIPTIVE ANALYSIS.

We will summarise the main dependent variable through proportions. This summary will be stratified between intervention and control PHTs.

We will also stratify these analyses by the covariates (BHA type and terciles of socioeconomic status).

BIVARIATE ANALYSIS.

We will test the difference in prescribed ASA proportions between the PHTs of intervention and control by chi-squared test. When in any cell, the expected number of events is <5, we will be using Fisher's exact test.

We will also stratify these analyses by the covariates (BHA type and terciles of socioeconomic status).

MULTIVARIATE ANALYSIS.

A logistic regression will be used to assess the intervention. The dependent variable will be the percentage of unjustified ASA prescriptions, the independent variable will be an indicator of intervention/control and we will control for all the covariates.

We will assess interactions between the intervention and the covariates.

6.9 WORKPLAN & CHRONOGRAM.

PRINCIPAL RESEARCHERS: Joel Domene Ojalvo (JDO), Pascual Solanas Saura (PSS), Àngels Pellicer Jacomet (APJ).

COLLABORATORS: family medicine physicians and nurses in the above-mentioned PHTs (Arbúcies-Sant Hilari Sacalm, Banyoles, Bàscara, Besalú, Blanes, Camprodon, Girona 2 - Can Gibert del Pla, Canet de Mar, Celrà, Figueres, La Jonquera, Llançà, Girona 3 - Montilivi/Vila-roja, Olot, Pineda de Mar, Ripoll, Roses, Salt, Sant Feliu de Guíxols, Girona 1 - Santa Clara, Santa Coloma de Farners, Sarrià de Ter, Sils-Vidreres-Maçanet de la Selva, Girona 4 - Taialà, Tordera and Vilafant). The present study will last a total of 1 year and 3 months and it will follow the stages described below:

- STAGE 0. Protocol design (November 2020 - January 2021).
  - This stage is completed and consisted on bibliographic research, protocol development and its presentation to a court of teachers at Faculty of Medicine, University of Girona, Spain.

- STAGE 1. Ethical evaluation of the protocol and protocol translation - (February - March 2021).
  - Study proposal to IDIAP Jordi Gol Ethics Comittee and expected acceptance.
  - Since the present protocol is in English, it will be translated into Catalan & Spanish.

- STAGE 2. ICS Girona regional management office approval (*Gerència Territorial de l'Institut Català de la Salut a Girona*) and Pilot study execution - (April 2021).
  - Since protocol will be in English, it will be translated into Catalan & Spanish.
  - All the information will be gathered and sent to ICS Girona Health Region PHT Direction so that they approve our trial and let us execute it.
  - Pilot study will be carried out in Montilivi PCC.

- STAGE 3. Correction of the study design according to the result of the pilot study - (May-June 2021)

- According to the obtained results of the pilot study, we will correct or modify the study design and intervention.

- STAGE 4. Sessions preparation and contact with intervention Primary Health Directions - (July-August 2021)
  - The content of each educational session will be prepared and filmed.

- STAGE 5. Startup of the trial - (September 2021 - December 2022).
  - Every 3 months an educational booster session will be carried out, so that interventions PHT members may remember ASA indications, through clinical cases. Each session will have some minutes to solve the doubts and questions of the participants, in which the main researchers of the trial will be available to do so.
  - We will carry out an educational intervention to a PHT every week.
    - September, October and November 2021: First educational session
    - December 2021, January and February 2022: First educational booster session.
    - March, April and May 2022: Second educational booster session.
    - June, September and October 2022: Third educational booster session.
  - During July and August 2022, educational booster sessions will be delayed to September 2022 due to lack of staff (holidays period).
  - There will be a monthly feedback to the PHT with its global data on unjustified ASA deprescription, which will be sent to each PHT direction.
  - Data will be collected until December 2022 so that time elapsed by the first and last educational intervention is the same among all PHTs.

- STAGE 6. Statistical and data analysis - (November, December 2022 and January 2023).
  - The main researchers will process the data with the adequate software. A multivariate analysis will be used so as to examine the contribution of confounding variates.
- STAGE 7. Results and writing - (January 2023).
  - Investigators will receive the analysed data from the statistical and will conduct the interpretation of obtained results. Thus, they will draft a conclusion and start writing the final formal article.

- STAGE 8. **Publication & diffusion - (From February 2023).**
  - Results and conclusions of our research will be sent to several scientific journals.

>> TABLE 9. **CHRONOGRAM.**

TASK	November 2020 - January 2021	February-March 2021	April 2021	May-June 2021	July-August 2021	September 2021 - December 2022	November, December 2022 and January 2023	January 2023	From February 2023
STAGE 0: **Protocol design**									
STAGE 1: **Ethical evaluation. Translation.**									
STAGE 2: **Approval by ICS Girona regional management office. Pilot study.**									
STAGE 3: **Modification of the intervention, if necessary**									
STAGE 4: **Sessions preparation and contact with PHT directions**									
STAGE 5: **Startup of the trial**						> SPECIFIC CHRONOGRAM			
STAGE 6: **Statistical and data analysis**									
STAGE 7: **Results and writing**									
STAGE 8: **Publication and diffusion**									

> STAGE 5: **STARTUP OF THE TRIAL - PHT EDUCATIONAL SESSIONS THROUGHOUT 2021 AND 2022**

	September 2021	October 2021	November 2021	December 2021	January 2022	February 2022	March 2022	April 2022	May 2022	June 2022	July 2022 August 22	September 2022	October 2022
1W	Girona 3				Figueres				Girona 1				Girona 1
2W	Pineda				Camprodon La Jonquera				Bàscara Tordera				Bàscara Tordera
3W	Sils				Girona 2				Banyoles				Banyoles
4W	Llançà Vilafant				Besalú Sta Coloma								
1W		Figueres				Girona 1				Girona 3			
2W		Camprodon La Jonquera				Bàscara Tordera				Pineda			
3W		Girona 2				Banyoles				Sils			
4W		Besalú Sta Coloma								Llançà Vilafant			
1W			Girona 1				Girona 3						
2W			Bàscara Tordera				Pineda						
3W			Banyoles				Sils						
4W							Llançà Vilafant						
1W				Girona 3				Figueres				Figueres	
2W				Pineda				Camprodon La Jonquera				Camprodon La Jonquera	
3W				Sils				Girona 2				Girona 2	
4W				Llançà Vilafant				Besalú Sta Coloma				Besalú Sta Coloma	

DATA SOURCE: **Own elaboration.**

6.10 ETHICAL & LEGAL DISCUSSION.

Medical research must always abide by the basic principles of ethics (autonomy, beneficence, non-maleficence and justice), since they are essential to follow any study procedure.
Firstly, beneficence and non-maleficence principles will remain unaltered since this study does not aim to amend the doctor-patient relationship: it will remain unchanged. Secondly, the principle of authonomy patients will not be compromised on patients: we do not aim to impose any medication change or pass over patients' opinion. This study only pretends to inform and form health care providers, by transmitting knowledge and training them, by providing them with those necessary tools adjusted to the current reality of prescription. Therefore, we want to convey a piece of clinically rellevant information to the health care provider and with that, the professional will respect the patient's autonomy. Justice will also be respected since we are not giving any information that excludes a certain group of people based on their religion, socioeconomic status, ethnic group, among others.
But, not only will we respect principles of ethics regarding patients, but also with health care providers, in this case, PHTs. No PHT has been excluded because of any predetermined criterion based on religion, ethnics, immigration rate… PHT autonomy will also be thoroughly respected since any intervention PHT will be able to decline its participation in this trial. Without doubt, beneficence and non-maleficence will also be valued, seeing that we want to try to attain is inform and train health care providers with knowledge based on evidence.

This trial also guarantees the confidentiality given that patients' data will be anonymous. Every healthcare provider will only have access to the data of his or her patients. Registered data in the clinical record by the healthcare provider will be anonymously collected and modified by ECAP clinical data station, so that we have specific cluster global data and in addition, individuals will not be able to be identified. Since we will not analyse individual data, we will not ask for an informed consent.
Monthly feedback will be sent to every PHT with its data, just as it is done with other PHTs indicators, such as SARS-COV-2 positivity tax. PHTs will not be able to access to other's PHT data.

The present project will be conducted following national and international ethics laws and principles:

- *Ley Orgánica 15/1999, del 13 de Diciembre, de Protección de Datos de Carácter Personal.*
- *Ley Orgánica 41/2002, del 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.*
- *Llei 16/2010, del 3 de juny, de modificació de la Llei 21/2009, del 29 de desembre, sobre els drets d'informació concernent la salut i l'autonomia del pacient, i la documentació clínica.*
- WMA Declaration of Helsinki - Ethical Principles for Medical Research involving Human Subjects, June 1964. Last revision in 64th WMA General Assembly, Brazil, October 2013.
- Spanish Medical Code of Ethics, Organización Médica Colegial, 2018.
- Good Clinical Research Practice in Health Sciences Research, Catalan Institute of Health, *Guia de bona pràctica en la recerca en ciències de la salut de l'ICS. Second edition, July 2015.*

Once this protocol is finished and before starting the project, it is planned to be presented to Clinical research ethical committees (IDIAP Jordi Gol), which is the organ in charge for assessment of ethical aspects of research carried out at a primary healthcare level.

The principal researchers of this study have no conflict of interests or any potential ones. They will not receive any payment for the tasks that they will carry out in this study.

6.11 BASELINE DATA.

Before sending this protocol to the Bachelor's thesis tribunal, we have not been able to collect baseline data, which would have counted the number of unjustified ASA prescriptions in different PHTs. Main resarchers will try to include these data in the thesis defense, which are expected to be available by then.

6.12 DISCUSSION.

The primary objective of this study is to assess whether a structured intervention is able to guarantee the quality of ASA prescription in primary health care in 65 and older population, by health care providers, family medicine physicians and nurses.

An improvement in quality of ASA prescription could be derived from two situations:

- Unjustified ASA prescription is due to the fact that it had not been prescribed according to current guidelines and it was considered a PPI.
- Unjustified ASA prescription turned out to be incorrectly labeled in the clinical record, or directly, not labeled.

If we achieved to improve the number of ASA prescriptions labelled as PIPs, this would imply that this patient could hypothetically benefit from the fact of preventing risks due to the deprescription of this medication. Nonetheless, let's suppose that our intervention concludes that the majority of those unjustified ASA were only a problem of registry. One could think that our intervention, then, has been somehow useless, since we have not found a PIP. However, this is simply not true.

On one hand, we may achieve that a significant number of diagnostic labels end up being registered in the clinical record of some patients, since, perhaps, they indeed needed to take ASA because of a determinate cardiovascular condition. This, would entail, without a shadow of doubt, that these patients could be benefited from this simple act: maybe that person should be taking other medications for this same condition, since it is common in cardiovascular secondary prevention treatments, for instance, or other diseases, and thus, we would be solving a PPO. An incorrent registry could also make some health care providers to pause ASA, taking into account that there is not a linked labelled diagnosis in their clinical record and harm this patient. Thus, a low quality clinical registry is not beneficial for the patient.

One could also wonder why this specific ASA PIP can still exist. This could be explained by therapeutic inertia. As we have already discussed before, ASA in primary prevention trials have been undergoing in the last 30 years and recent findings have entailed a change in prescription tendency, especially since ARRIVE, ASCEND and ASPREE outcomes came out. Consequently, guidelines and their recommendations have also been changing throughout these years. Thus, certain ASA prescriptions may not still be updated with these recent recommendations.

Regarding the design of this trial, the reader may think why have not we chosen a specific PHT, by applying this intervention and assess it. However, it would have been difficult to execute it and, probably, would have entailed a lot of bias, such as Hawthorne effect. Moreover, one PHT is not representative, each of them has special features: the number of assigned population (2100 in Cornudella de Montsant PHT to 63.000 in Terrassa E PHT), the area type (is the PHT in a rural or urban environment?), the socioeconomic level of it, the number of physicians and nurses working in it, among others. Hence, we thought that an ecological study, which would take into account several PHT, clusters, would be the best option, since our final goal is to extrapolate our results and to check out whether they could be implemented in our health region.

One could also wonder why we did not choose a before-and-after study, which would have been presumably much easier to carry it out. However, we opted for an intervention trial because, otherwise, we would not have had a control group. We have the need to know how our environment, the rest of PHT in our region, is behaving and whether it is also changing or not. All in all, without a control group, we would not know if our results would have been caused by our intervention, by chance or because an external factor has been affecting the whole population, thus, affecting the way that ASA is prescribed.

It could be reasonable to think why we did not accomplish this study by applying explicit or implicit deprescribing criteria, such as STOPP-START, which may already include ASA as primary prevention deprescription in elderly, for instance. However, the quality of evidence by several studies which assess these criteria is low [12], even when the study is a RCT. Furthermore, some of them present several potential bias. As a matter of fact, these studies tend to carry out complex interventions, in which they intend to manage a lot of medications. At the same time, this is very time-consuming, which could be simply unfeasible, even more nowadays taking into account our current health care situation.

Furthermore, the majority of family medicines practices use ECAP and this same clinical data station has included *Self-audit* tool, which, as above-mentioned, already incorporates a lot of these criteria. Thus, revising lists of medications one by one would have been, probably, useless.

Moreover, as we have already discussed, we cannot assert that all the unjustified ASA prescriptions in our environment are due to a lack of indication, for instance. We estimate that a relevant percentage of these PIP may be attributed to a wrong registry into ECAP,

with a wrongly labelled diagnosis, and, thus, it would be interesting to know the exact number of the problem, since there is barely bibliography on the topic. Our intervention, thusly, aspires not only to try to improve the patients' treatment management but also the diagnosis, by improving the quality of medical records.

Although we aim to reduce a considerable number of not correctly indicated ASA, a 50%, it would be reasonable to think why do not we intend to cut it to a nearly 0%. The reason of this decision is that, according to some authors, it exists a ceiling effect, in other words, despite the evidence base of intervention, inappropriate prescribing continues [81, 82]. For instance, an old person with angina pectoris will be automatically prescribed ASA and whilst medical tests are being undertaken, this person will be taking it. Thus, it is not possible to reach a 0% and that is why our goal is a 50% decrease.

In the end, our study pretends to deal with a specific medication problem. Hence, if it were proven as useful, a specific strategy could be implemented throughout Catalonia so as to tackle with this problem. Perhaps ECAP clinical data station could include a warning of this PIP and later to check out whether this intervention has achieved a greater ASA quality prescription.

RANDOMIZATION DISCUSSION.

We decided to randomise according to 2 categories: BHA area type and socioeconomic status. Although we had planned to choose more categories, we ruled it out since we only had 26 available PHT to randomise, and that would have entailed to create a lot of blocks that would have remained empty, without an intervention or control group. For this reason, we chose these two categories, which seemed to us important to take into account in this study due to the heterogeneity of PHT in our region.

Regarding to BHA area type, we planned to use a more specific and current classification, which classified PHTs into four categories (rural/semirural/semiurban/urban). This classification would have taken into account these special features that our PHT has (many times, a same BHA has not either a rural or urban population, but a semirural or semiurban one). However, again, if we had used this classification, we would not have been able to carry out randomization [>> ANNEX 10].

In terms of socioeconomic status, there were several options on the table. On one hand, we knew that MEDEA index (Mortality in small areas of Spain and socioeconomic and environmental inequalities) is frequently used in primary health care. It is a deprivation index which is built upon a census tract and it is based on six indicators:
manual workers population, temporary wage-earning population, unemployment, two insufficient education indicators (in people over 16 years old and in people between 16 and 29 years old) and homes without Internet access. On the other hand, there was a more recent index called ISC index (socioeconomic composite index), which takes into account similar indicators (exemption of pharmaceutical copayment, income < 18.000€, income >100.000€, manual workers population, insufficient education level, mortality before 75 years old and potentially avoidable hospitalisations).
Both had advantages and disadvantages. Firstly, MEDEA index did not convince us since, whilst it is validated in our country, it is not validated for rural areas. A lot of our analyzed PHTs were, indeed, rural. ISC, however, is validated for urban and rural areas, although it is still better correlated with urban ones [>> ANNEX 11 and 12]. From the latter indicator, we also like that is frequently used within the Catalan Health Service.

These indexes, then, combine socioeconomic indicators from census tracts, which afterwards, they are grouped according to their BHA. ISC, however, incorporates an additional variable, that is the exemption of pharmaceutical copayment, which is an individual variable, since it measures the proportion of individuals in a BHA which have this exemption. The rest are ecological variables.

These indexes, however, have two additional important limitations. On one hand, these included variables in the index are extracted at a census tract level, the last Spanish population census dates from 2011, which is a serious limitation. On the other hand, labour market variables are indicators that are field-based and this entails a limitation, since in our country, these variables do not represent gender: women do not participate in labour market and, then, they are not represented.
That's why we finally opted for using the average income per person, which is an income direct measure and it is based on recent data, specifically, 2019. Thus, the *Instituto*

Nacional de Estadística estimated this measure based on income tax return.

In order to make easier randomization, BHA were ordered into terciles. The higher tercile implied a worse socioeconomic status.

7. STRENGTHS & LIMITATIONS.

Our study has several strengths:

- It is a randomised controlled trial, that is an experimental and analytic study, which will have a control group and will allow us to assert that if there is a significative change in the ASA quality prescription in our intervention groups, it will be owing to our educational action and not to any external factor.
- The sample size of our study are all those PHTs managed by the Catalan Institute of Health, which have a wide range of diversity of features: from BHAs which cover highly-populated cities to BHA with a very sparse population; PHTs with a high income to a low income population. Hence, it allows us to be more representative of the reality throughout all Catalonia and, thus, even be somewhat comparable.
- The high prevalence of unjustified ASA within our health region with nearly a 6% of individuals taking it, making it an everyday problem in the daily practice, and, thus, letting us room for improvement.
- We aim to improve the quality of medical care, by improving the quality of treatment and even diagnosis, entailing that this study could be completely assumed by different PHTs and there is no need to invest any extra money.
- It is potentially one of the first studies to be conducted that intends to measure the wrong registry of ASA prescription and its linked indication.
- We plan to incorporate a pilot study following MRC guidelines so that our final educational intervention is feasible, whilst the majority of published studies did not include them.
- Our intervention will be dynamic, adapted to our health care reality: the content of our educational intervention will be changed according to the PHTs doubts and necessities.
- Our study has a feasible primary objective that if achieved, could imply an attainable application to the medical practice.

Nonetheless, this trial also has limitations:

- Blinding will not be possible due to the intended methodology.

- The fact that a Hawthorne effect could be given, since a lot of healthcare providers coincide during holidays in other PCCs or hospitals and could influence the way control group professionals prescribe ASA. We will try to minimise it by comparing it to a national contemporaneous group.
- Due to the pandemic situation, some PHTs could refuse to collaborate in our study. Hence, we have chosen 15 PHTs as intervention groups and not 13, which would be half of the included PHT within the trial.
- Basic health areas may have within it a big heterogeneity socioeconomically speaking. For instance, Girona 3 - Montilivi/Vila-roja BHA has 35.740 assigned inhabitants, 6.000 of which approximately live in one of the lowest income neighbourhoods in the whole region (Vila-roja), whilst Montilivi is one of the highest income ones. [76]

8. OTHER INFORMATION.

8.1 BUDGET.

The mission of this budget is to estimate the real cost of the execution of this study to the Catalan Institute of Health, the healthcare provider in our selected PHTs, since the majority of the tasks that this study implies will be or either done by the main researchers or by the same healthcare workers and, thus, will already be included in the work hours of all of them.

>> EXPENSES: STAFF SERVICES.

On the basis that there are approximately 6000 patients taking unjustified ASA in these 26 PHT and taking into account that there are approximately 500 Basic care unit (BCU), we can assert that each BCU will have to manage an average of 12 patients. Thus, we estimate that time which has to invested in every patient so as to determine whether his or her ASA is unjustified and to explain him/her the need of the deprescription might be of 25 minutes maximum each one, since professionals will have already received online tuition on this topic. Thus, we estimate that every BCU will invest not more than 5 hours so as to deal with all assigned patients taking unjustified ASA. We also have to keep in mind that not only family medicine physicians will take responsibility on this issue, but also nurses, since they are the other indispensable half of a BCU and can help to identify possible candidate patients and educate them on the need of ASA deprescribing.

Hence, to calculate the budget, we have assumed that not all PHTs will be intervention groups, only half of them, that is 250 BCU, approximately, and every BCU will need 5 hours with these patients, having a final number of 1250 hours. Thus, 1250 hours will be needed so as to manage patients in our study. We have also presupposed that 1000 hours will be invested by family medicine physicians and nurses (500 hours each group), 40 hours left will be assumed by PHT family medicine physician and nurse clinical referents and 10 by pharmacology experts in Girona Primary Healthcare Direction.

We have also appraised that primary healthcare attention residents will invest 200 hours on these patients, especifically 150h physician residents and 50h nurse residents. This difference on hours is due to the fact that the number of nurse residents is fewer than doctor residents.

PHT clinical coordinators, both physician and nurse reference, who may receive doubts and questions on ASA topic, in fact, already earn an extra payment due to this function that they carry out in their PHT or may conversely have an extra free time because of this. Thus, we will not pay an extra money to them.
On the other hand, pharmacology experts working in Girona Health Region Primary Healthcare Direction might also receive more complex questions on the topic by PHT clinical references. However, we expect that these will not be too frequent and will not be exceedingly time-consuming because questions will already be filtered. Likewise, the doubts that these experts may receive are also covered by ordinary work hours and they will not be paid a special pay.

All in all, since these tasks that this study entail, in fact, may be defined as an improvement of medical care quality, which is already an objective of the Catalan Institute of Health family medicine and nursing specialists, we expect that the Catalan Institute of Health assumes all these staff services expenses.

>> EXPENSES: OTHER EXPENSES.

Data will be provided by ECAP database and since they are public data upon request, as long as our project is approved by Ethics Comittee and the Girona Health Region Primary Healthcare Direction, we will not have to pay for this service. It is expected that administration staff working in this area will also assume the management of ECAP data (sending of raw data, periodic feedback to PHT, among others).

Statistical analysis of this study is simple and very defined. Thus, the same main researchers will assume this task and will be using free software so as to do so. We supposed that, at least, 12 hours will be needed.
We intend to publish our study in several journals, such as *Atención Primaria*, an indexed Spanish journal on primary healthcare or the *British Medical Journal*.
Thus, although our budget has a result of -43.612,90€, due to the earlier reasons, it will be reduced to - 4664,6 euros, that is the publication charges of those journals to which we would like to send our trial and translators' service so as to translate our patients' leaflets.

This budget also includes a contingence fund, a 10% of the total expenditures, which is usually recommended so as to be able to cope with unexpected but necessary expenses. Lastly, we have been pessimistic with this budget. Hence, although family medicine physicians and nurses base salary may be variable, as stated in the budget, we have made calculations taking into account the highest wage. Resident doctors and nurses salaries are also variable, which is due to the formation year in which that healthcare professional is. Since senior residents are those which already have assigned patients and work within primary healthcare centres, we have taken into account their salaries.

> FUNDING.

Since this study barely entails expenses and these expenditures are only planned so as to publish the results in scientific journals, we do not plan to bid for a grant, since the rules for these grants typically cover research-specific expenses. Thus, in order to cover these costs, we will write a specific request to the following institutions asking for a determinate sum of money:

- *Agrupació de Ciències Mèdiques i de la Salut de Girona.*
- *Societat Catalana de Medicina Familiar i Comunitària.*
- ICS Girona regional management office (*Gerència Territorial de l'Institut Català de la Salut a Girona.*
- Girona Region Primary Health care Direction (*Direcció d'Atenció Primària Girona*).
- Girona 3 - Montilivi/Vila-roja PHT Direction
- *Col·legi Oficial de Metges de Girona.*

If these bodies refused to give us a specific amount of money, the main researchers of the study will asume the cost of publication.
Regarding translation expenses, we will also try that they are covered by the hypothetic sum of money granted by these institutions. Furthermore, for this specific purpose, we intend to contact with the *Diputació de Girona*. If these options were not valid, the principal researchers will contact with several acquaintances who could translate these leaflets into the already mentioned languages.

>> TABLE 10. **STUDY BUDGET.**

CONCEPT	ESTIMATED PRICE	AMOUNT	EXPECTED INVESTED TIME	SUBTOTAL	REMARKS
> INCOME					
SUBTOTAL INCOME			**0 €**		
> EXPENSES					
1. MATERIAL					
eCAP database access Management of eCAP data by Primary Healthcare Direction administration staff†.	None. 15,98€/hour	- 24 months [January 2021 to December 2022]	- 30 hours	479,4 €	Expected to be assumed by the Catalan Institute of Health (*ICS*)
2. STATISTICIAN SERVICES					
Data analysis	30€/hour	-	12 hours	360 €	Assumed by main researchers
3. MEETINGS					
2-hours monthly coordination meeting among the 3 main researchers	20€/hour	27 months [November 2020 to January 2022]	54h · 3 researchers = 162h	3240 €	Assumed by main researchers
1-hour monthly online educational meeting with PHT	25€/hour	12 months and 3 weeks [September 2021 to October 2022]	44h · 3 researchers = 132h	3300€	
4. PUBLICATIONS					
Publication in *Atención Primaria* (journal), being Spanish Family Medicine association (semFYC) members.	610 €	-	-	610 €	-
Publication in *Annals of Family Medicine* (journal)	0€	-	-		-
Publication in *The British Medical Journal*	3934,4€ (£3500)	-	-	3934,4€	-
Pharmacoepidemiology & Drug Safety	0€	-	-		-

CONCEPT	ESTIMATED PRICE	AMOUNT	EXPECTED INVESTED TIME	SUBTOTAL	REMARKS
5. STAFF SERVICES					
PRIMARY HEALTHCARE ATTENTION SPECIALISTS†					
Family medicine physician salary	18,11 to 21,21€/hour		500h	10.605€	Expected to be assumed by the Catalan Institute of Health (*ICS*)
PHT family medicine physician clinical reference salary supplement	4,38€/hour		20h	6555€	
Family medicine nurse salary (DUI)	13,11 to 15,81€/hour		500h	7905€	
PHT family medicine nurse clinical referent salary supplement	0,313€/hour	-	20h	225,9€	
Pharmacy expert (Girona Primary Healthcare Direction - *DAP*)	18,42€/hour		10h	184,2€	
				117€	
PRIMARY HEALTHCARE ATTENTION RESIDENT PROFESSIONALS†‡					
Family medicine resident physician salary	8,01 to 10,25€/hour		150h	1537,5€	
Family medicine resident nurse salary	6,80 to 7,53€/hour		50h	376,50€	
TRANSLATORS	30€/hour	4 required languages	4h	120€	Not expected to be assumed by ICS
6. ETHICAL COMMITTEE APPROVAL					
IDIAP Jordi Gol Ethics Committee	0 €		-		
7. CONTINGENCY FUND					
10% of the expected expenses	4063 €			4063 €	
SUBTOTAL EXPENDITURES			**43.612,9 €**		

RESULT	**-43.612,9 €**

DATA SOURCE: **2020 Catalan Institute of Health Pay Rates (*Llistat de retribucions 2020, Personal Estatuari de l'Institut Català de la Salut*).**

†: salaries are based on base wage according to 2020 Pay Rates by the Catalan Institute of Health without including other salary supplements, taking into account 14 months salary and 37,5-hour workweek.

‡: despite resident salary varies according to the formation year, we will consider the highest wage, since it entails the final residence year and it is when residents work in the primary healthcare centre without supervision.

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10. ANNEXES

>> ANNEX 1.

>> ANNEX 1: DEPRESCRIBING RAINBOW: DETERMINANTS.		
CLINICAL DETERMINANTS	PSYCHOLOGICAL DETERMINANTS	SOCIAL DETERMINANTS
NNT Potential medicines-related benefit vs harms Expected time until benefit Person's prognosis Types of medicines Presence or absence of symptoms Availability of alternatives Knowledge of clinician Ethical considerations	Health beliefs or attitudes about medication and illness Cognitive function Knowledge Health and medication literacy Personal preferences for health outcomes	Influence of family, friends Social support, loneliness Burden of taking multiple medications Responsibilities Living conditions
FINANCIAL DETERMINANTS	PHYSICAL DETERMINANTS	
Health insurance Cost of medications Available resources	Pill burden Difficulty taking medicines Filling repeat prescriptions ADE Quality of life/self-rated health Comorbidities	
DATA SOURCE: [43]		

>> ANNEX 2.

>> ANNEX 2: UNADVISABLE MEDICATIONS IN OVER 75 YEARS OLD PATIENTS ACCORDING TO SELF-AUDIT TOOL.					
ATC.	ACTIVE INGREDIENT.	RISK/PRODUCED EFFECT	RECOMMENDATIONS/ADVICE	ALTERNATIVE	ATC.
A03A: DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS					
A03AB06	OTILONIUM BROMIDE.	Risk in older patients: excitation, agitation, somnolence, confusion. Important response to anticholinergic secondary effects .	Unfavourable benefit/risk. There are safer alternatives such as analgesics or anti-inflammatories.	Paracetamol Ibuprofen	N02BE01 M01AE01
A03F: PROPULSIVE MEDICATIONS.					
A03FA01	METOCLOPRAMIDE	Extrapiramidal effects and late dyskinesia risk.	Avoid use, except for gastroparesis.		
A06AA: SOFTENERS, EMOLLIENTS					
A06AA01	PARAFFIN.	Aspiration and adverse effects risk, especially among bedridden, psychiatric diseases or disabled patients.	Consider osmotic laxatives use.		
A06AA51	PARAFFIN COMBINATION.				
A10B: HYPOGLYCAEMIC MEDICATIONS (EXCEPT INSULINS).					
A10BB01	GLIBENCLAMIDE.	Long half-life sulfonylureas may cause long serious hypoglycemias.	Gliclazide or glipizide are first election sulfonylureas.	Glimepiride Gliclazide Glipizide	A10B22 A10BB09 A10BB07
B01A: ANTITHROMBOTIC MEDICATIONS.					
B01AC05	TICLOPIDINE.	Blood dyscrasia risk	There are safer and more effective alternatives. As dual anti platelet, ASA combined with clopidogrel or ticagrelor.	ASA, clopidogrel	B01AC06, B01AC04
B01C07	DIPYRIDAMOLE.	Orthostatic hypotension risk.		Clopidogrel/ ASA	B01AC30
B01AC22	PRASUGREL.	Major exposition to prasugrel active metabolite in over 75 years patients.		Ticagrelor	B01AC24
C02A: CENTRAL ACTION ANTIADRENERGIC AGENTS.					
C02AB01	METHYLDOPA	Central nervous system adverse effects risk. It may cause bradycardia and orthostatic hypotension.	Neither advisable as first line medication nor combined. To evaluate the need of treatment according to the therapeutic objective of the patient. To evaluate first-option hypotensive drugs according to comorbidities.	Enalapril Lisinopril Ramipril	C09AA02 C09AA03 C09AA05
C02AC01	CLONIDINE				
C02AC05	MOXONIDINE				

C02C: PERIPHERAL ACTIONS ANTIADRENERGIC AGENTS.					
C02CA01	PRAZOSIN	Orthostatic hypotension, especially in very old patients	To evaluate the need of treatment according to the therapeutic objective of the patient. To evaluate first-option hypotensive drugs according to comorbidities. In prostatic benign hyperplasia, to evaluate the use of tamsulosine.	Enalapril Lisinopril Ramipril	C09AA02 C09AA03 C09AA05
C02CA04	DOXAZOSIN				
G04CA03	TERAZOSIN				
C04A: PERIPHERAL VASODILATORS					
C04AD03	PENTOXIFYLLINE	Falls and orthostatic hypotension risk	Without proven efficacy		N02BE01 M01AE01
C04AE02	NICERGOLINE	Not proven efficacy. Unfavourable benefits/risk	Avoid its use		
C04AE04	DIHYDROERGOCRISTINE	Lack of evidence. Fibrosis risk cannot be ruled out.	-		
C04AE54	COMBINED DIHYDROERGOCRISTINE				
C07A: BETA-BLOCKER AGENTS					
C07AA07	SOTALOL	Beta-blocker with an additional antiarrythmic effect	Advisable to use cardioselective beta-blockers (metoprolol, bisoprolol, carvedilol)	Metoprolol Bisoprolol Carvedilol	C07AB02 C07AB07 C07AG02
G04B: UROLOGICALS					
G04BD02	FLAVOXATE	Anticholinergic effects risk, sedation and weakness	Due to its adverse effects, it is advisable to prioritize non-pharmacological measures (pelvic exercises) or to use minimum doses. Mirabegron is not either an adequate alternative due to its cardiovascular adverse effects. Oxibutinin: its effectivity in tolerated doses for elderly is questionable.		
G04BD04	OXIBUTININ				
G04BD06	PROPIVERINE				
G04BD07	TOLTERODINE				
G04BD08	SOLIFENACIN				
G04CA53	TAMSULOSIN AND SOLIFENACIN				
G04BD09	TROSPIUM CHLORIDE				
G04BD11	FESOTERODINE				
G04BD13	DEFESOTERODINE				
L02A: HORMONES AND RELATED AGENTS					
L02AB01	MEGESTROL	Minimum effect on weight. Increase in thrombotic events risk.	Only indicated in oncologic patients with anorexia-cachexia. To evaluate thrombotic risk and avoid its use in high risk cardiovascular patients.		

M03B: MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS					
M03BA03	METHOCARBAMOL	Anticholinergic effects risk	Its effectivity at tolerated doses for elderly is questionable		
M03BX02	TIZANIDINE				
M03BX08	CYCLOBENZAPRINE				
N02C: ANTIMIGRAINE PREPARATIONS					
N02CA52	ERGOTAMINE, COMBINATIONS	Peripheral vasoconstriction and cardiac ischaemia risk	To use other antimigraine drugs		
N05B: ANXIOLYTICS and N05C: HYPNOTICS AND SEDATIVES					
	SHORT-ACTING AND MEDIUM-ACTING BENZODIAZEPINES				
N05BA08	BROMAZEPAM	Prolonged sedation, falls and fractures, psychotic effects, irritability, cognitive deterioration, depression	When the use of benzodiazepines is indispensable, use low doses of lorazepam and lormetazepam. Use minimum effective dose and during as little time as possible. Dose increases and withdrawal should be gradually done.	Lormetazepam Lorazepam	N05CD06, N05BA06
N05BA12	ALPRAZOLAM				
N05BA14	PINAZEPAM				
N05CD05	TRIAZOLAM				
N05CD08	MIDAZOLAM				
N05CD09	BROTIZOLAM				
N05CD11	LOPRAZOLAM				
	LONG-ACTING BENZODIAZEPINES				
N03AE01	CLONAZEPAM	Prolonged sedation, falls, fractures, psychotic effects, irritability, cognitive deterioration, depression	When the use of benzodiazepines is indispensable, use low doses of lorazepam and lormetazepam. Use minimum effective dose and during as little time as possible. Dose increases and withdrawal should be gradually done.	Lormetazepam Lorazepam	N05CD06, N05BA06
N05BA02	CHLORDIAZEPOXIDE				
N05BA05	CLORAZEPATE DIPOTASSIUM				
N05BA09	CLOBAZAM				
N05BA10	KETAZOLAM				
N05BA01	DIAZEPAM				
N05BA51	DIAZEPAM, combinations				
N05CD01	FLURAZEPAM				
N05CD10	QUAZEPAM				
N05CA01	MEDAZEPAM and AMITRIPTYLINE				

	NON-BENZODIAZEPINE HYPNOTICS				
N05CF02	ZOLPIDEM	Risk of falls and fractures, increase in reaction time, psychiatric reactions and cognitive deterioration	Use minimum effective doses and as little time as possible. Dose increases and withdrawal should be gradually done.	Lormetazepam Lorazepam	N05CD06 N05BA06
N05CF01	ZOPICLONE				
N06A: ANTIDEPRESSANTS					
	TRICYCLIC ANTIDEPRESSANTS				
N06AA12	DOXEPINE	Anticholinergic adverse effects, sedation, orthostatic hypotension, risk of falls	Use first-line major depression drugs (SSRIs are first-line in geriatrics, such as citalopram or sertraline, SNRIs) and only tricyclics when other alternatives are not possible	Citalopram Sertraline	N06AB04 N06AB06
N06AA02	IMPRAMINE				
N06AA04	CLOMIPRAMINE				
N06AA10	NORTRIPTYLINE				
N06AA06	TRIMIPRAMINE				
	SSRI				
N06AB03	FLUOXETINE	Risk of central adverse effects (nausea, insomnia, dizziness and confusion)	To evaluate first-line SSRI in geriatrics: citalopram and sertraline	Citalopram Sertraline	N06AB04 N06AB06
N06AB05	PAROXETINE	Risk of anticholinergic effects, orthostatic hypotension, increase in convulsions and fractures	To evaluate first-line SSRI in geriatrics: citalopram and sertraline		
N06B: PSYCHOESTIMULANTS AND NOOTROPICS					
N06BX03	PIRACETAM	Without proven evidence	It requires regular evaluation of creatinine clearance so as to check if it is necessary to adjust the dose		
R03D: OTHER ANTI-ASTHMATICS FOR OBSTRUCTIVE AIRWAY DISEASES					
R03DA04	THEOPHYLLINE	Adverse effects risk due to narrow therapeutic margin	In case of monotherapy for COPD, there are safer and more effective alternatives		
OTHER MEDICINES					
M01AX21	DIACEREIN	Not advisable in >65 years due to hepatotoxicity risk and diarrhoea	It is advisable to stop it when diarrhoea is present. It is necessary to monitor the appearance of hepatic alteration signs and symptoms and it should not be used un patients with a hepatic disease.		

N03AA02	PHENOBARBITAL	High-risk of dependence, tolerance as a sedative and overdose risk	To evaluate the reduction of posology according to adverse effects. It is advisable to carry out clinical control, with plasmatic levels monitorization. To evaluate other antiepileptic or sedative drugs according to indication.		
R06A: ANTIHISTAMINES FOR SYSTEMIC USE					
	FIRST GENERATION ANTIHISTAMINES				
R06AB01	BROMPHENIRAMINE	Anticholinergic effects. Dizziness, somnolence, sedation, confusion, hypotension, hyper excitability, mouth dryness, blurry vision, urinary retention, glaucoma precipitation, tachycardia, palpitations, photosensitive reactions. Tolerance when used as hypnotics. Promethazine could potentiate extrapyramidal effects	Use preferably non-anticholinergic second-generation antihistamines (cetirizine, loratadine) Avoid its use during a long time (more than a week). Diphenhydramine could be used in acute cases of serious allergic reactions	Cetirizine Loratadine	N06AB04 N06AB06
R06AA02	DIMENHYDRINATE				
R06AA09	DOXILAMINE				
R06AA52	DIFENHYDRAMINE, COMBINATIONS				
R06AB02	DEXCHLORPHERNIRAMINE				
R03DA12	MEPIRAMINE				
R06AD01	ALIMEMAZINE				
R06AD02	PROMETHAZINE				
R06AD07	MEQUITAZINE				
R06AE05	MECLIZINE	Anticholinergic effects. Dizziness, somnolence, sedation, confusion, hypotension, hyper excitability, mouth dryness, blurry vision, urinary retention, glaucoma precipitation, tachycardia, palpitations, photosensitive reactions. Tolerance when used as hypnotics. Promethazine could potentiate extrapyramidal effects	Use preferably non-anticholinergic second-generation antihistamines (cetirizine, loratadine) Avoid its use during a long time (more than a week). Diphenhydramine could be used in acute cases of serious allergic reactions	Cetirizine Loratadine	N06AB04 N06AB06
R06AE92	CLOCINIZINE in ASSOCIATION				
R06AX02	CYPROHEPTADINE				
R06AX17	KETOTIFEN				
N05BB01	HYDROXYZINE				
DATA SOURCE: UNADVISABLE MEDICATIONS IN PATIENTS OVER 75 YEARS OLD, MEDICATION COORDINATION AND STRATEGY UNIT, CATALAN INSTITUTE OF HEALTH.					

>> ANNEX 3.

>> ANNEX 3: 15 MOST DISPENSED MEDICATIONS AMONG PATIENTS ABOVE 65 YEARS OLD IN GIRONA ICS PHTs		
ATC.	ACTIVE INGREDIENT.	NUMBER OF DISPENSED MEDICATIONS (NUMBER OF PACKAGINGS).
N02BE01	PARACETAMOL	427.191
A02BC01	OMEPRAZOL	419.361
C10AA01	SIMVASTATIN	293.096
B01AC06	ASA	256.636
A10BA02	METFORMIN	189.426
C09AA02	ENALAPRIL	175.706
C07AB07	BISOPROLOL	159.480
C03CA01	FUROSEMIDE	153.514
C10AA05	ATORVASTATIN	149.848
N05BA06	LORAZEPAM	149.026
C08CA01	AMLODIPINE	145.839
C03AA03	HYDROCHLOROTHIAZIDE	119.424
N02BB02	METAMIZOLE	109.414
C09CA01	LOSARTAN	98.112
N05CD06	LORMETAZEPAM	98.087
DATA SOURCE: ECAP (provided by *Technical Secretary and Clinical Development Area of Territorial Management of the Catalan Institute of Health)*		

>> ANNEX 4.

>> ANNEX 4. TOP 15 MEDICATIONS ENTAILING HIGHEST COST IN GIRONA ICS PHTs		
ATC.	ACTIVE INGREDIENT.	DISPENSED NET AMOUNT (EUROS).
C10AA05	ATORVASTATIN	2.486.376,48
B01AF02	APIXABAN	1.829.114,34
A10AE04	INSULIN GLARGINE	1.578.539,73
C09DX04	VALSARTAN AND SACUBITRIL	1.585.454,12
A10BD07	METFORMIN AND SITAGLIPTIN	1.496.724,66
N02AB03	FENTANYL	1.352.148,21
R03BB04	TIOTROPIUM BROMIDE	1.189.813,49
A02BC01	OMEPRAZOL	1.114.828,33
B01AF01	RIVAROXABAN	1.041.310,50
B01AB05	ENOXAPARIN	1.048.799,36
R03AL04	INDACATEROL AND GLYCOPYRRONIUM BROMIDE	937.224,99
G04CA02	TAMSULOSIN	872.437,86
N02BE01	PARACETAMOL	860.827,66
S01ED51	COMBINATIONS WITH TIMOLOL	849.072,26
R03AK06	SALMETEROL AND FLUTICASONE	814.834,12
DATA SOURCE: ECAP (provided by *Technical Secretary and Clinical Development Area of Territorial Management of the Catalan Institute of Health)*		

>> ANNEX 5.

>> ANNEX 5. CLINICAL CASES PRESENTATION ON ASA PRESCRIPTION

ACCESS: [FILE]

DATA SOURCE: Own elaboration.

>> ANNEX 6.

>> ANNEX 6. INFORMATION LEAFLET TO HEALTHCARE PROVIDERS.

S/Sistema de Salut de Catalunya

Salut/Institut Català de la Salut

Repensant la medicació del pacient
PER MILLORAR LA SEVA SALUT

àcid acetilsalicílic (aspirina)

- **En persones majors de 65 anys, l'àcid acetilsalicílic pot estar indicat com a tractament en prevenció primària si el pacient presenta algun dels següents diagnòstics** (segons la 10ª edició de la Classificació Internacional de Malalties, CIE-10)**:**
  - **D68.62 - Síndrome d'anticoagulant lúpic**
  - **E10 Diabetis mellitus tipus 1**
  - **G.45 - Atacs d'isquèmia cerebral transitòria i síndromes afines**
  - **H34.10 - Oclusió d'artèria central de la retina**
  - **I20-I25: Cardiopatia isquèmica**
  - **I21.9 - Infart agut de miocardi**
  - **I60-I69 - Malalties cerebrovascular**
  - **I70: Aterosclerosi**
  - **I80.3 - Flebitis i tromboflebitis a extremitats inferiors**
  - **I80.9 - Flebitis i tromboflebitis a lloc inespecífic**
  - **M32.9: Cèl·lules del lupus eritematós**
  - **Z95.2: Implant de vàlvula cardíaca (funcional) protètic**
  - **Z95.3: Implant de vàlvula cardíaca (funcional) xenogènic**

- **Indicar àcid acetilsalicílic en una persona major de 65 anys com a prevenció primària sense cap de les patologies prèvies comporta més riscos que beneficis:**
  - **Risc d'hemorràgia gastrointestinal i altres hemorràgies extracranials**
  - **Risc de sagnat intracranial**
  - **Sense benefici clínic pel pacient**

✓ **No cal un periode de retirada gradual de l'àcid acetilsalicílic**

preguntar està bé!

POTS ADREÇAR ELS TEUS DUBTES AL REFERENT CLÍNIC DEL TEU EAP

quina evidència demostra això?

- **L'estudi ASPREE (ASPirin for the Reduction of Events in the Elderly) es va publicar el 2018:**
  - Població de l'estudi**: Persones majors de 70 anys**
  - Mida de la mostra: **Assaig clínic randomitzat amb 20.000 pacients i un seguiment de 5 anys.**
  - Taxa d'esdeveniments cardiovasculars adversos majors: **10%**

Es va concloure que els pacients que prenien àcid acetilsalicílic com a prevenció 1ª:

- Tenien una mortalitat per qualsevol causa un 14% més alta que els pacients que no en prenien.
- La taxa d'hemorràgia era un 38% més alta respecte el grup control.
- L'aspirina no va reduir la taxa d'esveniments cardiovasculars adversos majors.

font:

- McNeil JJ, Nelson MR, Woods RL, et al. ASPREE Investigator Group. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med.2018 Oct 18;379(16):1519–1528.
- McNeil JJ, Wolfe R, Woods RL, et al., ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018 Oct 18;379(16):1509–1518.
- McNeil JJ, Woods RL, Nelson MR, et al. ASPREE Investigator Group. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med.2018 Oct 18;379(16):1499–1508.

altres preguntes freqüents

- **Els pacients d'edat avançada tenen un risc significativament més alt d'hemorràgia major. Les persones majors de 85 anys tenen fins a un 7% de risc anual d'hemorràgia.**
- **El risc d'hemorràgia gastrointestinal i altres hemorràgies extracranials s'incrementa per altres factors del pacient, com ara història d'úlcera o hemorràgia gastrointestinal prèvia, disfunció renal severa, medicacions concurrents, tabaquisme o ús d'alcohol.**
- **Les hemorràgies menors recurrents tenen un impacte significatiu en la qualitat de vida dels pacients.**

font:

- Primary Health Tasmania, Consultant Pharmacy Services, A guide to deprescribing: Aspirin, May 2019. Disponible a Internet: https://www.primaryhealthtas.com.au/wp-content/uploads/2018/09/A-Guide-to-Deprescribing-Aspirin-2019.pdf

>> ANNEX 7.

>> ANNEX 7. **INFORMATION LEAFLET TO THE PATIENTS.**

S/Sistema de Salut de Catalunya

Salut/Institut Català de la Salut

Repensant la seva medicació
PER MILLORAR LA SEVA SALUT

Els medicaments han tingut un gran impacte en ajudar-nos a mantenir-nos bé. A mesura que ens fem més grans, els nostres cossos canvien, així que és important assegurar que les nostres medicacions són encara adequades a nosaltres.

aspirina (àcid acetilsalicílic)

- **L'aspirina és efectiva en evitar que persones amb malalties prèvies de l'aparell cardiovascular tinguin recaigudes, com ara:**
  - **Diabetis tipus 1**
  - **Ictus o accidents cerebrovasculars (atacs de feridura)**
  - **Infart agut de miocardi (atac de cor)**
  - **Malaltia vascular perifèrica**
  - **Altres malalties del sistema cardiovascular**

- **Ara bé, prendre aspirina de manera diària sense cap de les malalties abans mencionades sent major de 65 anys comporta més riscos que beneficis:**
  - **Risc de sagnat digestiu**
  - **Risc de sagnat cerebral**
  - **Cap benefici per la seva salut**

El seu metge/-ssa i infermer/-a de família són les persones adequades per respondre preguntes sobre la seva salut

preguntar està bé!

modificat de:

- Primary Health Tasmania, Consultant Pharmacy Services, Rethinking your medications for better health outcomes. Disponible a Internet: https://www.primaryhealthtas.com.au/wp-content/uploads/2018/06/Rethinking-Your-Medications-consumer-brochure.pdf

>> ANNEX 8.

>> ANNEX 8: **PHT AREA TYPE (2020)**					
PRIMARY HEALTH TEAM NAME.	ASSIGNED MUNICIPALITIES.	MUNICIPALITIES POPULATION *(INHABITANTS)*	DENSITY *(INHABITANTS/Km²)*	DISCREPANCY SCORE	CLASSIFICATION
Arbúcies-Sant Hilari Sacalm	Arbúcies Sant Hilari Sacalm	6.608 5.703	72,90	0,615 0,486	RURAL
Banyoles	Banyoles Cornellà de Terri Porqueres Serinyà Esponellà Fontcoberta Sant Miquel de Campmajor Crespià	20.053 2.399 4.677 1.133 463 1.469 229 254	193,18	0,38 1,28	RURAL
Bàscara	Bàscara Garrigàs Palau de Santa Eulàlia Pontós Sant Miquel de Fluvià Camallera	1001 451 90 260 761 856	61,77	0,05 0,41	RURAL
Besalú	Besalú Argelaguer Maià de Montcal Montagut i Oix Sant Jaume de Llierca Tortellà	2487 296 463 930 871 818	45,86	0,09 0,30	RURAL
Camprodon	Camprodon Molló Setcases Llanars Sant Pau de Segúries Vilallonga de Ter	2.298 336 170 535 688 398	13,65	0,07 0,09	RURAL
Canet de Mar	Canet de Mar Sant Pol de Mar Sant Iscle de Vallalta Sant Cebrià de Vallalta	14865 5428 1342 3438	500,3	0,62 3,33	RURAL
Celrà	Celrà Bordils Juià Madremanya Sant Martí Vell Flaçà La Pera Sant Joan de Mollet	5561 1761 319 288 251 1130 435 498	107,41	0,12 0,71	RURAL

PRIMARY HEALTH TEAM NAME.	ASSIGNED MUNICIPALITIES.	MUNICIPALITIES POPULATION *(INHABITANTS)*	DENSITY *(INHABITANTS/Km²)*	DISCREPANCY SCORE	CLASSIFICATION
La Jonquera	La Jonquera Agullana Biure d'Empordà Boadella i Les Escaules Cantallops Capmany Darnius Maçanet de Cabrenys Pont de Molins La Vajol	3320 863 241 272 309 611 537 698 516 89	26,47	0,07 0,17	RURAL
Llançà	Llançà El Port de la Selva Portbou La Selva de Mar Colera	4775 958 1063 195 445	60,92	0,14 0,40	RURAL
Ripoll - Sant Joan de les Abadesses	Ripoll Sant Joan de les Abadesses Vallfogona de Ripollès Ogassa Les Llosses	10.803 3.224 196 240 212	44,54	0,29 0,29	RURAL
Roses	Roses Cadaqués Castelló d'Empúries Palau-saverdera Pau	19807 2695 11100 1456 557	232,94	0,71 1,55	RURAL
Sarrià de Ter	Sarrià de Ter Girona (Pont Major) Sant Julià de Ramis Cervià de Ter Sant Jordi Desvalls Viladesens Colomers	5229 2768 3576 966 760 206 174	250,2	0,18 1,66	RURAL
Sils-Vidreres-Maçanet de la Selva	Sils Vidreres Maçanet de la Selva Riudarenes	6219 7951 7066 2204	132,41	0,58 0,88	RURAL
Girona 4 - Taialà	Girona (Taialà, Domeny, Fontajau, Germans Sàbat) Sant Gregori Canet d'Adri Sant Aniol de Finestres	32.180	106,46	0,80 0,7	RURAL

PRIMARY HEALTH TEAM NAME.	ASSIGNED MUNICIPALITIES.	MUNICIPALITIES POPULATION *(INHABITANTS)*	DENSITY *(INHABITANTS/Km²)*	DISCREPANCY SCORE	CLASSIFICATION
Vilafant	Vilafant Albanyà Avinyonet de Puigventós Borrassà Cistella Lladó Llers Navata Ordis Sant Llorenç de la Muga Santa Llogaia d'Àlguema Siurana Terrades Vilamalla Vilanant	5421 155 1641 733 282 844 1237 1427 361 265 368 171 338 1161 386	47,6	0,09 0,31	RURAL
Blanes	Blanes	38.502	2152,15	3,85 14,34	URBAN
Girona 2 - Can Gibert del Pla	Girona (Can Gibert del Pla, Santa Eugènia, Sant Narcís)	32.180	-	-	URBAN
Figueres	Figueres Fortià Riumors El Far d'Empordà Vila-sacra	47.235 787 246 602 758	959,53	0,99 6,39	URBAN
Girona 3 - Montilivi/ Vila-roja	Girona (Montilivi, Vila-roja, Font de la Pólvora)	35.740	-	-	URBAN
Olot	Olot Les Preses Santa Pau	35.926 1855 1614	452,98	1,31 3,01	URBAN
Pineda de Mar	Pineda de Mar Santa Susanna	27984 3548	1269,87	1,57 8,46	URBAN
Salt	Salt Vilablareix Fornells de la Selva Aiguaviva Bescanó	32138 3063 2670 765 4991	582,76	0,87 3,88	URBAN
Sant Feliu de Guíxols	Sant Feliu de Guíxols Castell-Platja d'Aro Santa Cristina d'Aro	22097 11030 5287	337,04	1,28 2,24	URBAN
Girona 1 - Santa Clara	Girona 1 - Santa Clara (Barri Vell, Montjuïc, Mercadal)	22.578	-	-	URBAN

PRIMARY HEALTH TEAM NAME.	ASSIGNED MUNICIPALITIES.	MUNICIPALITIES POPULATION *(INHABITANTS)*	DENSITY *(INHABITANTS/Km²)*	DISCREPANCY SCORE	CLASSIFICATION
Santa Coloma de Farners	Santa Coloma de Farners Vilobí d'Onyar	13363 3333	160,18	1,66 1,06	URBAN
Tordera	Tordera Fogars de la Selva	17519 1469	152,3	0,94 1,01	URBAN
DATA SOURCE: [48] and [83]					

>> ANNEX 9.

>> ANNEX 9: PHT ACCORDING TO THEIR SOCIOECONOMIC STATUS (2019)			
PHT NAME.	ASSIGNED POPULATION (INHABITANTS).	AVERAGE INCOME PER PERSON. (In EUROS).	ASSIGNED TERCILE.
Figueres	48.988	10.236,3	1
Roses	32.645	10.448,44	1
Tordera	17.411	10.653,8	1
Pineda de Mar	29.677	10.704,8	1
Blanes	38.502	10.853,31	1
Sils/Vidreres/Maçanet de la Selva	22.531	10.879,82	1
Sant Feliu de Guíxols	35.514	11.108,53	1
Llançà	6.726	11.492,70	1
Arbúcies/Sant Hilari	12.265	11.549,12	2
Salt	42.314	11.688,21	2
Vilafant	14.226	11.720,12	2
Girona 2 - Can Gibert del Pla	32.180	11.740,5	2
Canet de Mar	22.992	11.816,4	2
La Jonquera	6.991	11.945,56	2
Santa Coloma de Farners	16.176	11.965,52	2
Bàscara	4.595	12.383,24	2
Girona 4 - Taialà	15.256	12.589,52	2
Besalú	6.172	12.652,53	3
Banyoles	32.101	12.799,41	3
Celrà	9.959	12.840,71	3
Olot	38.798	12.961,57	3
Sarrià de Ter	13.781	12.969,66	3
Camprodon	3.942	13.125,9	3
Ripoll - Sant Joan de les Abadesses	14.357	13.136,79	3
Girona 3 - Montilivi/Vila-roja	35.740	15.864,27	3
Girona 1 - Santa Clara	22.578	16.128,39	3
DATA SOURCE: [76]			

>> ANNEX 10.

>> ANNEX 10: PHT AREA TYPE ACCORDING TO ALTERNATIVE CLASSIFICATION (2020)					
PRIMARY HEALTH TEAM NAME.	ASSIGNED MUNICIPALITIES.	ASSIGNED POPULATION (INHABITANTS)	SURFACE (Km^2)	DENSITY (INHABITANTS/Km^2)	CLASSIFICATION (RURAL, URBAN, SEMI-RURAL, SEMI-URBAN)
Arbúcies-Sant Hilari Sacalm	Arbúcies Sant Hilari Sacalm	12.358	169,5	72,90	RURAL
Banyoles	Banyoles Cornellà de Terri Porqueres Serinyà Esponellà Fontcoberta Sant Miquel de Campmajor Crespià	32.397	167,7	193,18	URBAN
Bàscara	Bàscara Garrigàs Palau de Santa Eulàlia Pontós Sant Miquel de Fluvià Camallera	4.596	74,4	61,77	RURAL
Besalú	Besalú Argelaguer Maià de Montcal Montagut i Oix Sant Jaume de Llierca Tortellà	6.201	135,2	45,86	RURAL
Blanes	Blanes	38.502	17,89	2152,15	URBAN
Camprodon	Camprodon Molló Setcases Beget Llanars Sant Pau de Segúries Vilallonga de Ter	4.004	293,2	13,65	RURAL
Girona 2 - Can Gibert del Pla	Girona (Can Gibert del Pla, Santa Eugènia, Sant Narcís)	32.180	-	-	URBAN
Canet de Mar	Canet de Mar Sant Pol de Mar Sant Iscle de Vallalta Sant Cebrià de Vallalta	23.294	46,56	500,3	URBAN

Figueres	Figueres Fortià Riumors El Far Vila-Sacra	49.512	51,6	959,53	URBAN
La Jonquera	La Jonquera Agullana Biure d'Empordà Boadella i Les Escaules Cantallops Capmany Darnius Maçanet de Cabrenys Pont de Molins La Vajol	7086	267,6	26,47	RURAL
Llançà	Llançà El Port de la Selva Portbou La Selva de Mar Colera	6.726	110,4	60,92	RURAL
Girona 3 - Montilivi/ Vila-roja	Girona (Montilivi, Vila-roja, Font de la Pólvora)	35.740			URBAN
Olot	Olot Les Preses Santa Pau	39.591	87,4	452,98	URBAN
Pineda de Mar	Pineda de Mar Santa Susanna	29,677	23,37	1269,87	URBAN
Ripoll - Sant Joan de les Abadesses	Ripoll Sant Joan de les Abadesses Vallfogona Ogassa Les Llosses	14.495	325,4	44,54	SEMI-RURAL
Roses	Roses Cadaqués Castelló d'Empúries Palau-saverdera Pau	33.008	141,7	232,94	URBAN
Salt	Salt Vilablareix Fornells de la Selva Aiguaviva Bescanó	43.416	74,5	582,76	URBAN

Sant Feliu de Guíxols	Sant Feliu de Guíxols Castell-Platja d'Aro Santa Cristina d'Aro	35.514	105,37	337,04	URBAN
Girona 1 - Santa Clara	Girona (Barri Vell, Montjuïc, Mercadal)	22.578	-	-	URBAN
Santa Coloma de Farners	Santa Coloma de Farners Vilobí d'Onyar	16.550	103,32	160,18	URBAN
Sarrià de Ter	Sarrià de Ter Girona (Pont Major) Medinyà Cervià de Ter Sant Jordi Desvalls Viladesens Colomers	13.920	55,63	250,2	SEMI-RURAL
Sils-Vidreres-Maçanet de la Selva	Sils Vidreres Maçanet de la Selva Riudarenes	22.804	172,22	132,41	SEMI-URBAN
Girona 4 - Taialà	Girona (Taialà, Domeny, Fontajau, Germans Sàbat) Sant Gregori Canet d'Adri Sant Aniol de Finestres	15.426	144,89	106,46	SEMI-URBAN
Tordera	Tordera Fogars de la Selva	17.801	116,88	152,3	URBAN
Vilafant	Vilafant Albanyà Avinyonet de Puigventós Borrassà Cistella Lladó Llers Navata Ordis Sant Llorenç de la Muga Santa Llogaia d'Àlguema Siurana Terrades Vilamalla Vilanant	14.374	301,92	47,6	RURAL
DATA SOURCE: [48] and [83]					

>> ANNEX 11.

>> ANNEX 11: ISC INDEX ACCORDING TO PHT (2017)			
BASIC HEALTH AREA	ISC INDEX (2017)	CORRECTED ISC	SEPTILE
Tordera	3,431151	55,54	1
Salt	3,421852	55,39	1
Pineda de Mar	3,319533	53,73	2
Figueres	3,244627	52,52	2
Sils-Vidreres-Maçanet de la Selva	2,992343	48,44	3
Girona 2 - Can Gibert del Pla	2,921994	47,30	3
Ripoll	2,857738	46,27	3
Roses	2,822165	45,69	3
Arbúcies-Sant Hilari Sacalm	2,855786	46,23	3
Roses	2,822165	45,69	3
Blanes	2,753407	44,58	3
Llançà	2,703153	43,77	4
Sant Feliu de Guíxols	2,68817	43,52	4
Camprodon	2,673714	43,29	4
Vilafant	2,558899	41,43	4
Santa Coloma de Farners	2,544991	41,21	4
Girona 4 - Taialà	2,529603	40,96	4
Canet de Mar	2,491898	40,35	5
Besalú	2,484168	40,23	5
Bàscara	2,451159	39,69	5
La Jonquera	2,430393	39,36	5
Sarrià de Ter	2,338012	37,86	5
Celrà	2,329878	37,73	5
Olot	2,278718	36,90	5
Banyoles	2,139143	34,65	6
Girona 3 - Montilivi/Vila-roja	1,619731	26,25	7
Girona 1 -Santa Clara	1,309856	21,24	7
DATA SOURCE: [84]			

>> ANNEX 12.

>> ANNEX 12. CLASSIFICATION OF PHT ACCORDING TO ISC (2017)			
FIRST SEPTILE	SECOND SEPTILE	THIRD SEPTILE	FOURTH SEPTILE
Tordera Salt	Pineda de Mar Figueres	Sils-Vidreres-Maçanet Girona 2 - Can Gibert del Pla Ripoll Roses Arbúcies-Sant Hilari Sacalm Blanes	Llançà Sant Feliu de Guíxols Camprodon Vilafant Santa Coloma de Farners Girona 4 - Taialà
FIFTH SEPTILE	SIXTH SEPTILE	SEVENTH SEPTILE	
Besalú Bàscara La Jonquera Sarrià de Ter Celrà Olot	Banyoles	Girona 3 - Montilivi/Vila-roja Girona 1 - Santa Clara	
DATA SOURCE: [84]			

>> ANNEX 13.

>> ANNEX 13. TASMANIAN GUIDELINES MODIFICATION OBTAINED CONSENT

Joel Domene Ojalvo <jdomene6@gmail.com> jue, 14 ene 8:59 (hace 11 días)
para info

To whom it may concern,

I am writing in reference to a *guide to deprescribing: aspirin* that I have checked out on the primary health care Tasmania website.
My name is Joel Domene Ojalvo and I am a 6th year medical student from Girona, Spain and I am carrying out a final degree project on aspirin deprescription.

After having checked several resources on your website, I would be really grateful if you authorised me to translate the following guidelines into Spanish and Catalan languages so that I could include them in my final degree project:
- A guide to deprescription: general information
- A guide to deprescription: aspirin

Without a doubt, if you allowed me to do so, I would include the original source and your consent in my project.

Please, do not hesitate to contact me if you have any further questions or concerns,

Thanks in advance,

Kind regards,

Joel.

Translation of Deprescribing Recources Recibidos ×

Peter Tenni <peter.tenni@utas.edu.au> 0:56 (hace 7 horas)
para mí, Catherine

Hello Joel,
Apologies for the delay in responding.
Yes, Primary Health Tasmania will give permission for translation of the two guides (general deprescribing and aspirin) into Catalan and Spanish.
Could you please provide a copy of the completed translated guides when they are done.
Regards
Peter

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Consultant Pharmacist
Consultant Pharmacy Services
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May you be Happy, May you be Well, May you be Comfortable and at Peace