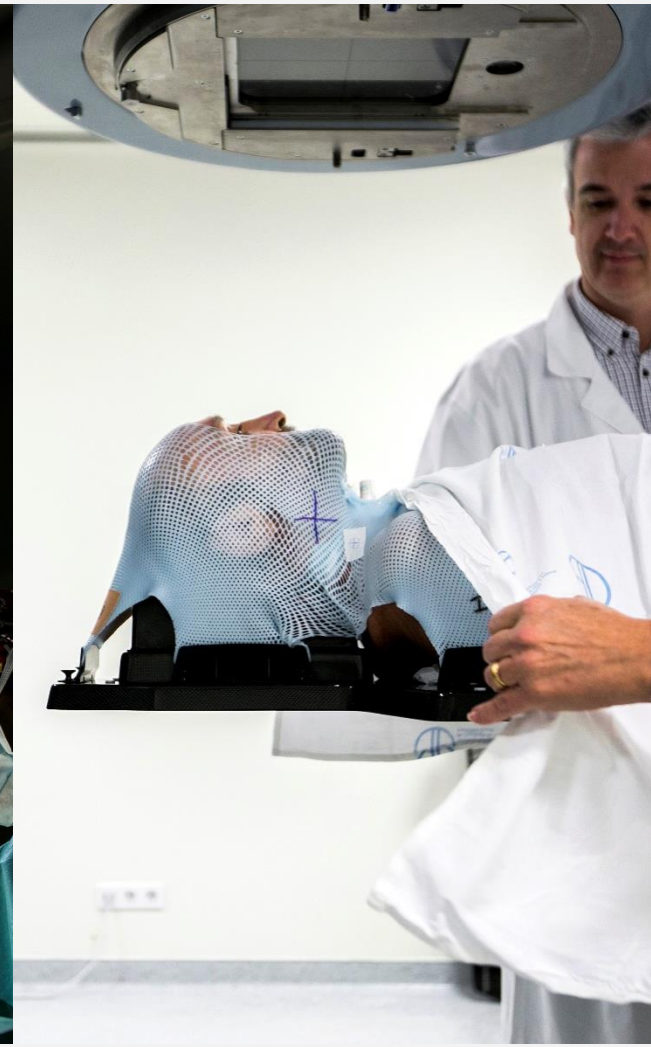
Pharmaceutical Consultation Project IPOLFG

Proposal | Consulting Lab 2018/2019



Glossary

Ambulatory Care	Provide services specifically for outpatients
Antineoplastic/Cytotoxic Drugs	Drugs used for cancer treatment, which work by preventing cell growth or replication
Concomitant Drugs	Two or more drugs taken at the same time
First-Line Treatment	Standard initial treatment for a given pathology, which provides the best results with the least possible side-effects
Markov-Chain	Model that describes the transition of events based on the present state of system
Outpatient	All patients who attend the hospital for treatment, but are not hospitalized
Therapeutic Adherence	The extent to which the medical prescription as a whole is followd by the patient
Therapeutic Ratio	Ratio between the toxic and therapeutic dosages of a active substance
Treatment Retention Rate	The probability of, by the end of each period, a patient who started on a specific treatment remains on the same
Tyrosine-Kinase Inhibitors	Enzymes used as componentes in the several anti-cancer drugs, they act by blocking the active of certain proteins

List of Abreviations, Acronyms and Initials

ACSS – Administração Central do Sistema de Saúde

AML - Acute Myeloid Leukemia

ARS – Administração Regional de Saúde

CLL - Chronic Lymphocytic Leukemia

CML - Chronic Myeloid Leukemia

DDIs - Drug-drug interactions

HESE – Hospital Espírito Santo de Évora

HGO – Hospital Garcia de Orta

IPO – Instituto Português de Oncologia

IV – Intravenous

MalMe - Malignant Melanoma

MC – Markov Chains

MCL - Mantle Cell Lymphoma

MMy - Multiple Myeloma

PC – Pharmaceutical Consultations

TDT – Therapy Diagnosis Technician

TRR – Treatment Retention Rate

TKI – Tyrosine-Kinase Inhibitors

WM - Waldenström Macroglobulinemia

Acknowledgements

We would like to thank **Rosário Sepúlveda,** by the time, patience and knowledge shared that could only be provided by someone who walks the line between Economy and Health

To **Doctor António Gouveia,** for his unmiserable expertise that has broaden our horizons in what concerns pharmacy

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To all members of **clinical staff of Hospital Garcia de Orta** and **Hospital Espírito Santo de Évora,** for the warm welcome in their institutions and availability to clarify all our doubts

"Healing is a matter of time, but it is sometimes also a matter of opportunity."

- Hippocrates

AGENDA

1. Executive Summary

Summary

Through the Consulting Labs organized by Professor Constança Casquinho of Nova School of Business and Economics, we were given the opportunity to write our Master's Thesis about a real project at *Instituto Português de Oncologia de Lisboa Francisco Gentil*. The goal of this project was to write a Business Plan that would show the economic viability of the implementation and expansion of Pharmaceutical Consultations at IPO's Pharmaceutical Ambulatory Care Unit. As a result, the project was written at this institution through the collaboration of Management and Finance students and with the constant support of professional Pharmaceutical staff.

Partners & Advisors

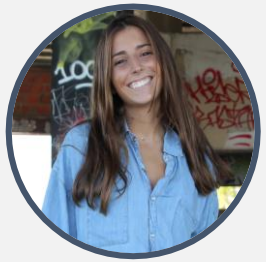
Partners:
- Dr. Mello Gouveia
- Dr. Rosário Sepúlveda
- Dr. Humberto Gonçalves
- Dr. Joana Russo

Advisor:
- Prof. Constança Casquinho

Team

Aadam Abdurramane

Guilherme Pipa



Madalena Oliveira

1. Executive Summary

IPO LFG

Founded in 29th of December 1923, IPO was created due to a need to investigate all aspects related to Cancer at a specialized institute, as well as to support patients with cancer-related problems.

Throughout the course of its history, IPO has always stood at the top of national standards by fulfilling its mission, with a multidisciplinary approach that follows the best clinical practices available, with the end goal of satisfying the needs of patients from the moment of diagnosis until the end of every course of treatment required.

Deliverables

The greatest challenges related to the project developed in the last 3 months can be split into two:

1. Verify if there is economic viability that explains the realization of Pharmaceutical Consultations and define the characteristics which optimize the model.
2. Define their future expansion path taking into consideration the pilot project.

Taking this into consideration, the project's deliverables can be summed into the following topics:

1. An analysis of the pilot project, with the goal of underlining its economical benefits, while also considering the clinical gains delivered to the patients.
2. A methodology (described in detail in **Annex 1**) which makes it possible to assess, in a systematic way, the benefits previously described when considering expanding the Pharmaceutical Consultations to new drugs, which takes the form of an excel document and an instruction manual.
3. A proposal for criteria to expand the Pharmaceutical Consultation in the short and long term, as well as guidelines to mitigate future stakeholder risks which can arise in the expansion of the P.C.

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2. Methodology

Challenge: What is the potential demand for pharmaceutical consultations?

Method: Taking into account that IPO is a public institution and the ethical constraints of restricting a service to only a sub-section of patients, it was not considered ethical by stakeholders to consider only certain patient demographics as potential demand for P.C. (e.g. only patients over a given age). Therefore, demand was assessed based on potential new drugs to be included in P.C. In order to establish which medication should be covered, we worked with IPO's pharmacists in order to establish which criteria should be used when selecting them. In order to confirm our choices, and seeing as doctors are the final decision-makers concerning clinical decisions and one of the key players regarding P.C., an in-depth interview was performed to assess which drugs they considered most relevant for including in P.C. in the short-term. Next, in order to create guidelines towards long-term expansions to the P.C., we worked with pharmacists to determine which selection criteria could be dropped and in what order, until only the ones that are core requirements for exploring the pharmacists' competences remain. At that point, a total of 36 drugs will be covered by these consultations. In this way, IPO's pharmacy will be able to increase the time spent giving these consultations according to their installed capacity, while prioritizing drugs with greater cost-saving potential and from which patients stand to reap the highest clinical benefits of pharmaceutical care. Additionally, by analysing all of the occasions in which pharmaceutical interventions were necessary throughout the pilot-project, which has been taking place since 2016, we observed that all but one of those events occurred within the patients' first 12 months of prescription. As such, and in order to generate the capacity to cover additional drugs without increasing personnel, we suggested that these consultations should only be mandatory for one year after beginning treatment for each patient, after which they would be subject to a need identified by either the doctor or pharmacist, or in case the patients themselves express a need for additional clarifications. In conclusion, the potential demand for pharmaceutical consultations includes all outpatients who take any of the 36 medicines mentioned above, for their first 12 months of prescription at the time that medicine is added to the portfolio of P.C.

2. Methodology

Challenge: What is the added financial value of pharmaceutical consultations? (1)

Method: In order to estimate the added financial value we focused firstly on an internal analysis performed for Ibrutinib patients within the first 4 months of treatment by Dr Joana Russo, which concluded that patients receiving additional pharmaceutical care in the form of these consultations would tend to remain longer with their 1st line treatment. We also learned that 2nd line treatments are often more effective but also significantly more expensive and toxic, and Ibrutinib's is one such case. Given this information and the support of literature sources, we had a need to find an analysis model which would allows us to better quantify and predict the cost savings obtained by having patients spend a longer period in the 1st line. After discussing this challenge with Prof Pedro Pita Barros, we chose to use Markov Chains, a model which takes the shape of a tree diagram, on which are represented the two scenarios of either maintaining 1st line treatment or advancing to 2nd line along pre-defined time periods, along with the respective probability of each scenario occurring. In order to use this method, we analysed data from every individual Ibrutinib patient's files, including their pathology, the first prescription date, the dates of all P.C. performed so far, and the date in which the patient advanced to the 2nd line treatment when applicable (in order to allow direct comparisons between data of patients who began treatment at different moments, all dates were normalized). Data from patients who were either included in PC after beginning treatment or had insufficient available records was excluded. We then used this data to calculate aggregated treatment retention rates (T.R.R.) for these patients in each time period across 12 months, with which it would be possible to build Markov Chains for Ibrutinib's pathologies. Each pathology was considered separately as the recommended dosages and expected patient outcomes differ significantly. We then performed a financial impact analysis comparing the directly built M.C. with a systematised version which assumed the average T.R.R .for every period, which would make it easier to perform future estimates. Next, we calculated the standard cost for IPO of a patient taking Ibrutinib vs its 2nd line treatment for a month, along with the incremental costs of performing P.C. Considering that P.C. occur in the Ambulatory services, where the only required resource is the incremental time, we compared this added time weight to the standard outpatient care. Thus, our group spent 5 days attending the several activities of outpatient care to build a clear picture of this sector, identifying 3 types of activities during its regular services, the data of which was then measured and registered. However, in the case of Ibrutinib, the additional time required was calculated but, seeing as Ibrutinib consultations were possible through merely reorganizing the pharmacists' tasks, we had to consider a null opportunity cost so far, as no additional personnel or space were necessary and no tasks had to be replaced. This process would allow us to compare total costs for scenarios with and without P.C. However, since Ibrutinib consultations began immediately after the drug was available at IPO and patients were gradually added to P.C., we lacked a stable control group to calculate specific financial benefits. We tried to mitigate this obstacle by requesting the same data we collected from an institution without P.C. (IPO Porto) and comparing the T.R.R. of patients from each institution. In the end this method was not possible due to ethical and confidentiality concerns, which would have delayed the reception of this data to a point beyond the time scope of this project. As such, we recommended that, for the next included medicines in P.C., patient outcomes without consultations should be registered across a longer time period, in order to allow comparisons in added value. For this end, we constructed an excel file and a detailed instruction manual, with which IPO's pharmacists will be able to easily calculate and compare expected cost savings for various different medications.

2. Methodology

Challenge: What is the added financial value of pharmaceutical consultations? (2)

Method: In addition to the previously mentioned study, Dr Joana Russo had identified a second source for financial value in the P.C., in the form of money saved from dosage adjustments which only occurred because the pharmacist was able to identify situations in which the patient's health could be jeopardised. In these situations, the pharmacists used data pertaining to the number of pills reduced per day and the length of the adjustment in order to reach the final amount of savings which resulted from each intervention. Taking this into consideration, we calculated the frequency of these interventions and the total savings they represented on a yearly basis. For this end, we collected additional data pertaining to all dosage alterations performed, making a distinction between those that occurred due to medical interventions and those that only occurred as a result of pharmaceutical intervention, and the variation in the number of pills taken per day as a result of each one. We then mapped the cases of pharmacist-recommended dosage adjustments against those performed by doctors, and observed that there was little overlap in each group's motives for reducing the dosage (medical adjustments were mostly related to the patients' response to therapy, as opposed to the detection of interactions with other drugs). Lastly, yearly savings due to dosage adjustments were calculated by considering the number of patients in each of Ibrutinib's pathologies covered by P.C., the average percentage of patients whose dose is adjusted through pharmacist counsel, and the average value of past interventions.

2. Methodology

Challenge: How to overcome possible obstacles in the expansion of Pharmaceutical Consultations?

Method: Two clear obstacles were identified: additional time required to conduct P.C. and the stakeholders' sphere of influence within IPO. Regarding the first, taking into consideration that the expansion of P.C. will overcome the installed capacity at some point, we assumed that the most efficient way to overcome this risk was to hire additional support. To do so, we firstly identified and mapped the many activities of the Pharmacy and Ambulatory Care. Following this, we interviewed 3 high-profile entities within the institution to assess the individual value of each activity. Afterwards, a sum of individual rankings was performed. In collaboration with the Head of Pharmacy, Dr. Melo Gouveia, we managed to identify activities whose delegation to a new hire would not damage the value chain within the Pharmacy. Finally, a comparative analysis of possible hiring positions was made.

Concerning stakeholders, as we assumed that the stakeholders within the Pharmacy would have better knowledge of the ecosystem, we decided to perform individual interviews to assess who were the main stakeholders potentially involved with the expansion of P.C., how they are related to each other and the level of power of each group. To evaluate the level of power, individual interviews were made to: the aforementioned Head of Pharmacy, Dr. Melo Gouveia, Dr. Humberto Gonçalves, Head of Outpatient Care and Dr. Rosário Sepúlveda, Director of Management Control Services. We believed that these 3 individuals reflected a heterogeneity of perspectives with the Pharmacy, as their status within IPO reflect an understanding of the influence of both internal and external stakeholders. Taking each perspective into consideration, we performed an average of each stakeholder's perceived power. Subsequently, to understand the interests of each stakeholder regarding P.C., we decided to interview individuals belonging to each internal stakeholder group. In order to have an unbiased estimation of their interests, in-depth interviews were performed, through which we sought to understand their knowledge, interest, advantages and disadvantages. Also, to further improve our analysis, we considered other sources, including informal interviews. For the stakeholders we could not interview, we assessed along with the members of the Pharmacy which would be their interests concerning the expansion of the pharmacy consultation. Finally, given the assessed power and interests, we ranked each stakeholder according to their degree of significance to the priorities of P.C. expansion.

AGENDA

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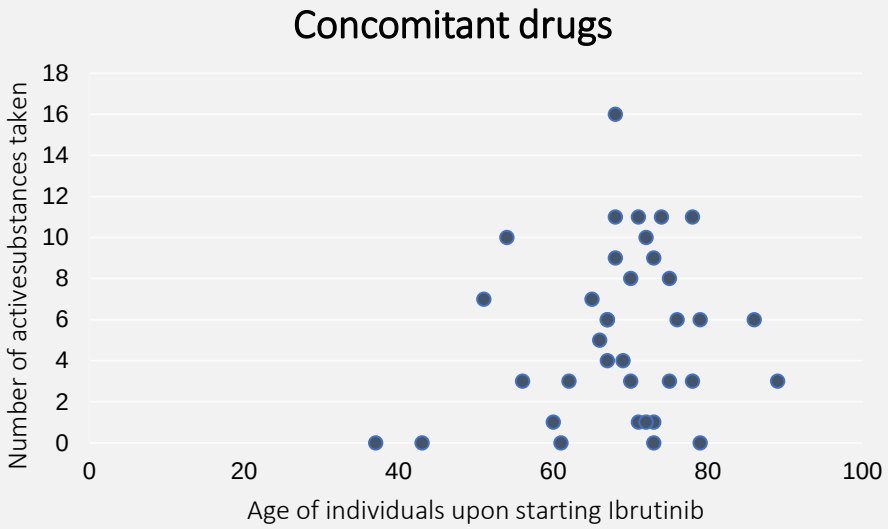
3 Diagnosis

i. Concomitant Drugs
ii. Development of Antineoplastic Drugs
iii. Ambulatory Cost Analysis
iv. Factors that Contribute to Antineoplastic Treatment Efficiency
v. Opportunity

Clinical staff must pay attention to the high levels of concomitant drugs taken by outpatients.

Diagnosis: Concomitant Drugs



- **Concomitant drugs** are defined as the consumption of medicines besides the ones prescribed
- As the sample highlights, this is a reality within IPO. Moreover, it is important to emphasize the high number of individuals with high levels of co-medication.
- Thus, it is essential to find out possible **DDIs** in the individuals taking oncologic treatments.

Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions[1]

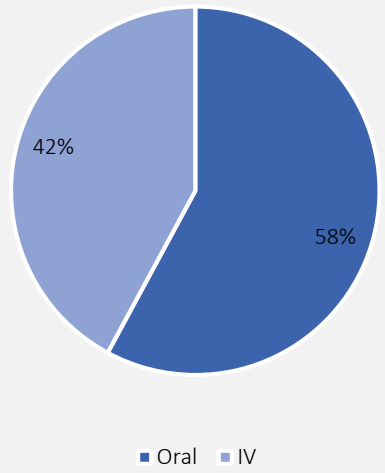
A study carried out at an ambulatory setting, with 302 patients of the hematology/oncology department starting new IV or oral anticancer treatment regimens, led to the identification of 603 DDIs, where 120 DDIs in 81 patients were considered potentially clinically relevant. Considering these 120 DDIs, 39 clinical interventions had already been performed by the hemato-oncologist, while 42 were recommended by the clinical pharmacologist. The number of comorbidities and "over-the-counter" drugs were identified as determinants.

[1] R. W. F. van Leeuwen, F. G. A. Jansman, P. M. L. A. van den Bemt, F. de Man, F. Piran, I. Vincenten, A. Jager, A. W. Rijneveld, J. D. Brugma, R. H. J. Mathijssen, T. van Gelder; Drug–drug interactions in patients treated for cancer: a prospective study on clinical interventions, *Annals of Oncology*, Volume 26, Issue 5, 1 May 2015, Pages 992–997, https://doi.org/10.1093/annonc/mdv029

The growing development focus on new oral antineoplastic medication presents clear benefits to patients' lifestyles but also challenges for the clinical bodies.

Diagnosis: Development of Antineoplastic Drugs

New Antineoplastic Active Substances IPO 2013-2017 (n=38)



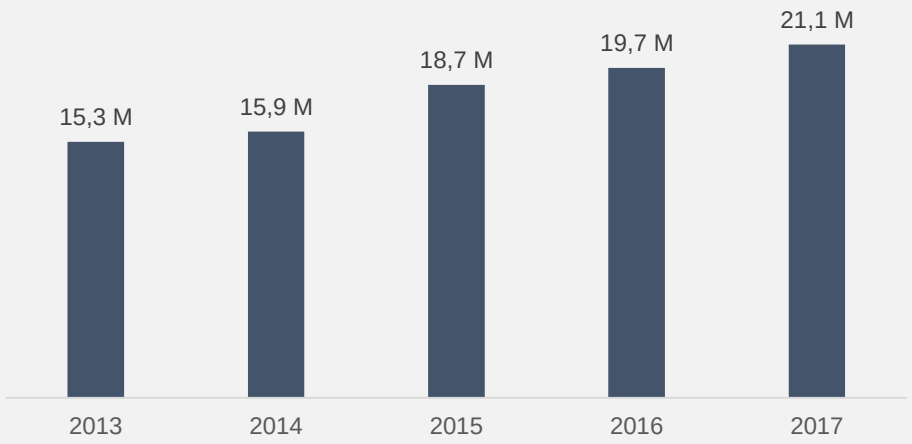
- **Cancer medication** has been gradually **shifting from a focus on IV therapy** as the number of oral formulations increases.
- Currently, around **25-35% of cancer drugs in development** are intended for **oral administration**. [1]
- This reality is corroborated by the proportion **of new antineoplastic active substances** which became regularly used **at IPO** in the last **5 years** – **58%** were meant to be **taken orally** and only **42%** were **intravenous**.
- As long as **IV and oral** medications are both **adequate** to a given **clinical situation** and their **efficacy is equal**, **patients** will tend to **prefer the oral option**[2] due to the following reasons:
  - ✓ Higher level of **control** over their treatment
  - ✓ More **convenience** as a result of less hospital visits for administering treatment
  - ✓ Better **quality of life**
  - ✓ Lower need for **invasive procedures**
- However, oral antineoplastic medication may present **challenges** to maintaining patients' **therapeutic adherence**:
  - ✓ Incapability of keeping track of **complex treatment regimens** at home
  - ✓ Experiencing unexpected intolerable **side-effects**
  - ✓ **Lack of communication** between the patient and the clinical body
  - ✓ **Insufficient supervision** checkpoints towards the patients' treatment progression

Source:
[1] McCullough, S., PharmD, & Newton, R., CPA. (2017, October 13). "Pharmacy's Changing Role as Cancer Care Transitions From Infused to Oral Therapies."
[2] Paolella, Gennaro A., et al. (2018, March 8). "Adherence to Oral Anticancer Medications: Evolving Interprofessional Roles and Pharmacist Workforce Considerations."

Drug consumption in IPO's Ambulatory service has steadily increased over the last five years, with a large part of this increase being the result of a reduced quantity of drugs.

Diagnosis: Ambulatory Cost Analysis

Evolution of spending in outpatient drugs



In the last years it is possible to verify that the expenditure by outpatients has increased significantly, at an annual arithmetic growth rate of **8,4 %**.

Throughout the last five years, costs have increased mainly due to:

- Increased use of **Lenalidomide**, which was a consequence of its expansion in the treatmentment of MM.
- Evolution of **VePCafenib+Cobimetinib** and **Dabrafenib+Trametinib** in the treatment of Malignant Melanoma.
- Evolution in the use of **Dasatinib** and **Nilotinib** as a 2nd line treatment of CML.
- Appearance of **Ibrutinib** in 2015 for the treatment of CLL, MCL, and WM.
- Evolution of **Posaconazole** for treatment of patients in prophylaxis with AML and in the Bone Marrow Transplant Department.

Lenalidomide, Ibrutinib and **Dasatinib+Nilotinib** are used in the treatment of hematologic diseases and, in 2017, they represented **38.4 %** of the spending in drugs for IPO outpatients.

More detailed consumption data for each of these medicines can be found in **Annex 2**.

Hematology patients represent a small fraction of total patients, but the spending per patient within this department is much larger that the average within IPO.

Diagnosis: Ambulatory Cost Analysis

Cost of drugs taken

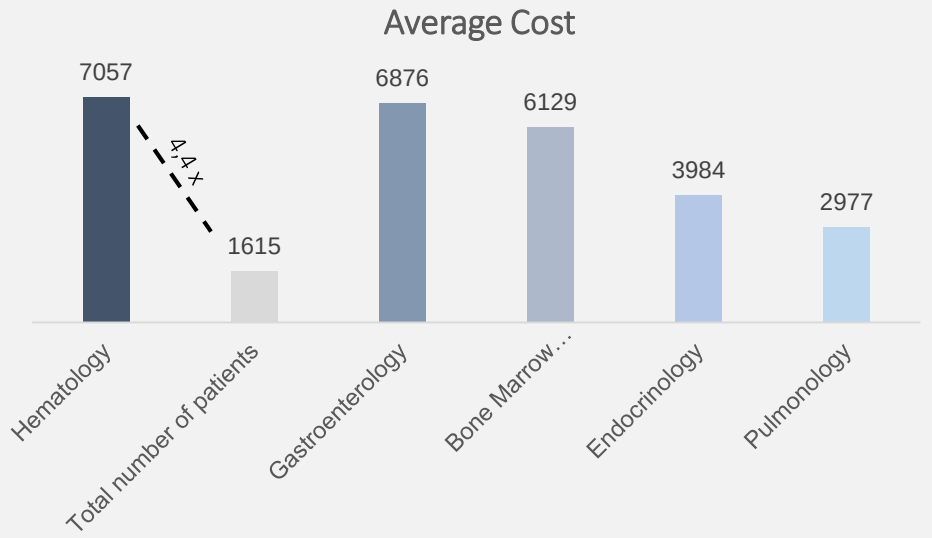
- In 2017, the cost of drugs related to Hematology represented **48.30%** of the total drugs for outpatients, while the total number of patients represented only **12.56%** of the sample.

Average cost by department

- Thus, the annual average cost of drugs distributed in Hematology is **4.60** times higher than the average cost per patient of the several medical departments in IPO.

Average cost per patient

- Aditionally, the average cost per patient in Hematology in 2017 was aproximately **4.40** times higher than the average cost per patient in the sample.



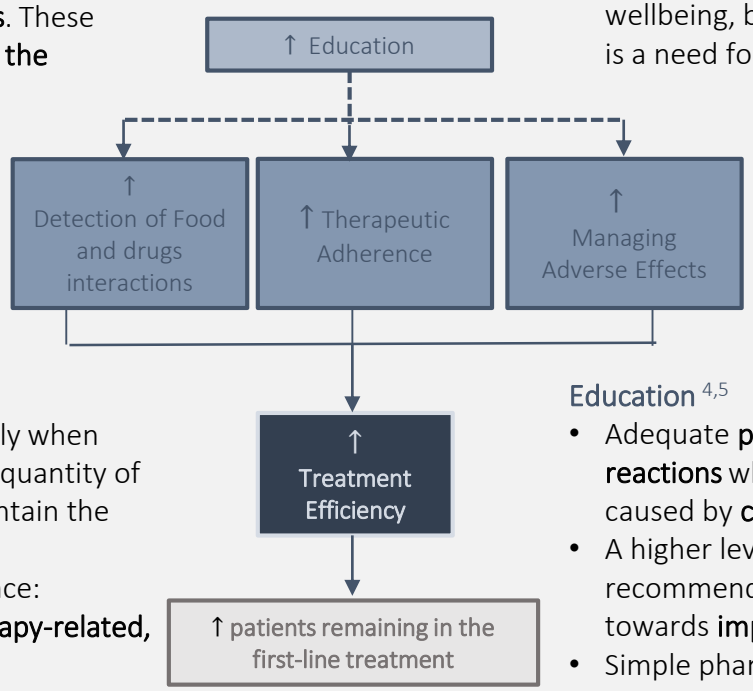
Disclaimer: the number of patients between each department is not mutually exclusive (e.g.: a patient can attend both the Pediatrics and Pneumology departments)

Detection of food and drug interactions, therapeutic adherence and adverse effect management are 3 factors which can influence the efficiency of oncological treatments. Patient education is a strong contributor to the outcomes of these factors.

Diagnosis: Factors that Contribute to Antineoplastic Treatment Efficiency

Drug and Food Interactions [1]

- **Many oral chemotherapies** not only have a **low therapeutic ratio** but their **absorption** can also be greatly affected by a wide range of interactions with other products, ranging from other **medications** to **common foods**. These possible interactions can negatively influence the **effectiveness of the treatment**, as well as harming the patients' wellbeing.



Managing Adverse Reactions 4

- When taking **oral chemotherapies,** patients experience **adverse effects** that can have a **high prevalence**. These adverse effects not only affect the patient's wellbeing, but can have an impact on the **discontinuation rate.** Therefore, there is a need for **managing adverse reactions** of **oral chemotherapy patients**.

Adherence [2,3]

- To achieve **favorable health outcomes**, adherence is vital. Especially when treating conditions in which it is important to administer a stable quantity of medication over fixed time periods, **adherence** is essential to maintain the **efficacy of the treatment** without **compromising its outcomes**.
- According to *Who*, there are five dimensions that impact adherence: **Sociodemographic, Health system-related, Condition-related, Therapy-related, and Patient-related.** (Annex XXX)

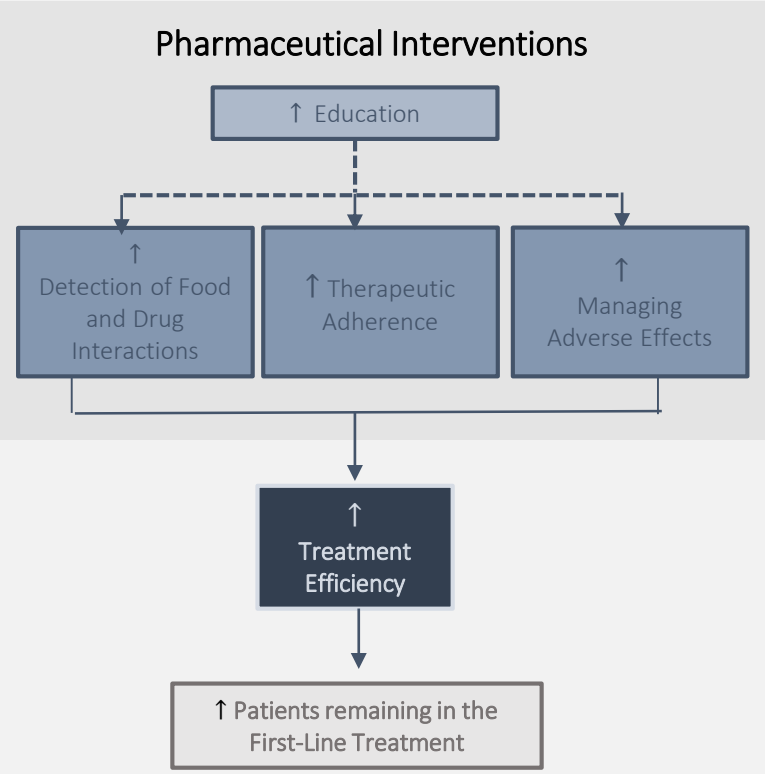
Education [4,5]

- Adequate **patient education** plays a **critical role** in helping them **avoid adverse reactions** which occur as a result of oral chemotherapy, mainly due to confusion caused by **complicated dosing regimens**.
- A higher level of **communication between the patient and pharmacist** has been recommended by the *National Comprehensive Cancer Network* as a measure towards **improving adherence** rates and **identifying safety concerns**.
- Simple pharmacist interventions towards **teaching** patients the **consequences of ingesting certain drugs concurrently** and getting them to avoid new medications before **discussing them with their doctor** could be a key factor in **avoiding dangerous drug interactions**.

Sources:
[1] Segal, E. M. et al. (2014, April 22). Oral Chemotherapy Food and Drug Interactions: A Comprehensive Review of the Literature.
[2] Mislang, A. R. et al. (2017, June). Adherence to oral cancer therapy in older adults: The International Society of Geriatric Oncology (SIOG) taskforce recommendations.
[3] World Health Organization. (2003) Adherence to Long-Term Therapies – Evidence for action.
[4] Backes, K., Griesbach, S., Wilhelm, S., & Plank, G. (2013, May 29). Identification of Drug Therapy Opportunities with Oral Chemotherapy.
[5] Riechelmann, R., & Girardi, D. (2016, April/May). Drug interactions in cancer patients: A hidden risk?

Literature suggests that pharmaceutical interventions' impact is significant concerning detection of DDIs, patient education, therapeutic adherence, and managing adverse effects. The study performed in this project happens as a consequence of these 4 factors.

Diagnosis: Factors that Contribute to Antineoplastic Treatment Efficiency



- Detection of DDIs:

A study carried out at the **hematology/oncology** department in the **Strasbourg University Hospital** between 2012 and 2013 studied the role of the clinical pharmacy services. By performing P.C. on **489 inpatients**, **4,393 prescriptions** were analyzed. As a result, in **12.6 %** of these prescriptions, there were **552** drug-related problems, with **14.3%** being related to **DDIs**, **11.7%** with **underdosing, 8.9%** to **overdosing**, and **2.5%** due to **side-effects.** From the total of drug-related problems, **96%** of interventions were accepted and implemented by the medical staff.

- Patient education

The oncology ward of a tertiary hospital affiliated with the **Southern Medical University** in **China** conducted a study to assess the efficiency of **pharmaceutical interventions** on the chemotherapy **knowledge-attitude-pratice** of cancer patients. **149 patients** were distributed randomly, with 77 being included in a group receiving **pharmaceutical counseling** throughout 2 months, while the remaining 77 were placed in a control group. To assess education, all patients answered a questionnaire in the beginning and end of the study. As a result, it was possible to verify a **statistically significant improvement in chemotherapy-related knowledge** in the group receiving **counseling.** [2]

- Therapeutic Adherence

Adherence in cancer disease is highly variable.[3] For instance, myeloma patients have difficulties in treatment adherence due to the complex regimes. Studies, such as the one developed in the University of Illinois at Chicago, propose that integrating a clinical pharmacist into a healthcare team is relevant, since providing education and improving patient-related symptoms may contribute to better adherence.[4] It has also been proposed that clinical pharmacists can improve adherence to oral therapies which can have better therapeutic outcomes.[5]

- Managing Adverse Reactions

A study performed at the municipal hospital of Gifu, in Japan, assessed the effect of pharmaceutical counseling on reducing instances of adverse effects. To evaluate this, a questionnaire was made between chemeotherapy cycles to **39 patients** with **breast cancer,** with 20 patients receiving pharmaceutical counseling, while the reimaining 19 were used as a countrol group. The results showed a **signficant decrease in some adverse effects (malaise and nausea)** in the group with **pharmaceutical counseling.**[6]

Sources:

[1] Delpeuch, A., Leveque, D., Gourieux, B., & Herbrecht, R. (2015, January). Impact of Clinical Pharmacy Services in a Hematology/Oncology Inpatient Setting.
[2] Wang, Y., Wu, H., & Xu, F. (2015, November 19). Impact of Clinical Pharmacy Services on KAP and QOL in Cancer Patients: A Single-Center Experience.
[3] Heins, M. et al. (2017, August 1). Adherence to cancer treatment guidelines: influence of general and cancer-specific guideline characteristics.
[4] Sweiss, K. (2018). Oral Antimyeloma Therapy: Barriers to Patient Adherence and Tips for Improvement.
[5] Felton M. et al. (2014, November 7). Medication adherence to oral cancer therapy: The promising role of the pharmacist.
[6] Tanaka, K. et al. (2018, April 30). Impact of pharmacist counselling on reducing instances of adverse events that can affect the quality of life of chemotherapy outpatients with breast Cancer.

Due to a number of factors, the current oncological environment provides an opportunity for a greater focus on pharmaceutical care.

Diagnosis: Opportunity

Growing development of antineoplastic drugs

- ✓ The paradigm shift towards an **increase** in oral **antineoplastic medication** presents the clinical body with a number of **challenges** in order to help patients keep track of their treatment regimens and manage side-effects at home

Economic Burden:

- ✓ There is an increasing **financial burden**, with **Hematology** as the **highest spender** in **outpatient drugs** due to the **treatments** required, along with the **high cost** of certain **individual drugs**.

Evident Risk Factors

- ✓ A significant number of cancer patients consume various amounts of **concomitant drugs** which must be constantly **monitored**

Improvement of Treatment Efficiency:

- ✓ Literature is clear that education, drug interactions, adherence, and managing adverse reactions can impact treatment **efficiency**. **Pharmacists** can **improve these outcomes**

Opportunity:

The current environment is one in which pharmaceutical care can function as a critical driver to improve the outcomes of cancer outpatients

AGENDA

AGENDA

4 Current Situation at Pharmacy Ambulatory Care

i. Pharmaceutical Outpatient Care – Pharmaceutical Consultation vs Regular Distribution
ii. Follow-Up Pharmaceutical Consultation
iii. Pharmaceutical Consultation - Internal Benchmarking
iv. Pharmaceutical Consultation - External Benchmarking

The Pharmaceutical Consultation allows engagement in fundamental topics for patient healthcare, which would not be possible through other means at the Hospital Pharmacy. However, these consultations represent a burden concerning time consumed.

Current Situation at Pharmaceutical Ambulatory Care: Pharmaceutical Consultation vs Regular Distribution

Pharmaceutical Consultation

1ST CONSULTATION (20 MIN)

- Patients are given a brochure with the goal of educating them in aspects such as drug administration, possible side-effects, food and dietary supplements to avoid, as well as details to the follow-up appointments.
- The pharmacist provides the contact of the ambulatory services with the goal of clarifying possible doubts.
- Therapeutic adherence is not measured, since it is the first appointment after the drug was prescribed.
- Potential DDIs are assessed through oral questioning.

FOLLOW-UP (15 MIN)

The patients are questioned as to their understanding of the following topics:

- **Drug compliance**
- **Drug-drug interactions**
- **Relevant adverse reactions**

Sometimes blood pressure and other health indicators of the patient are also analysed.

Regular Appointments

1ST APPOINTMENT (10 MIN)

- Clarification of relevant information concerning drug administration and possible side-effects.

AFTER DOSAGE ADJUSTMENTS (5 MIN)

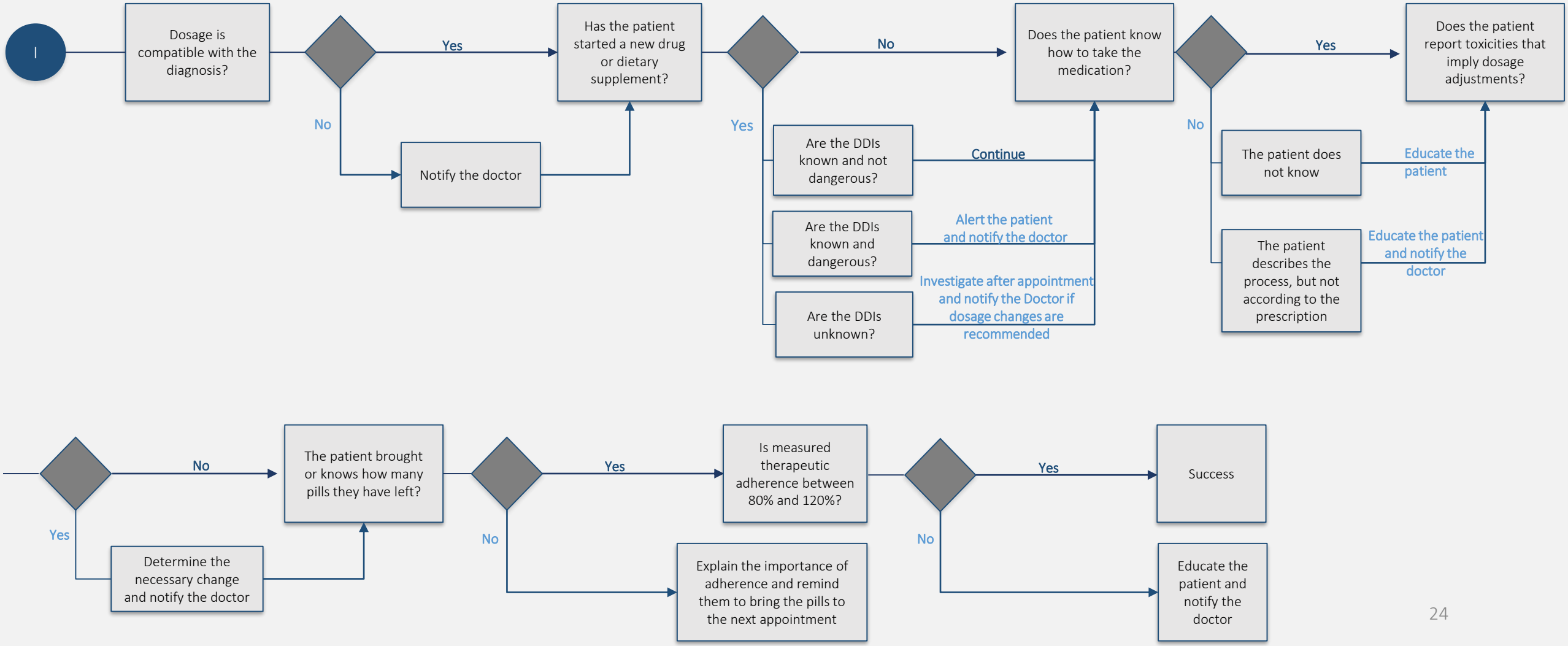
- The patient is given additional explanations with regards to the new dosage.

SIMPLE DISTRIBUTION (3 MIN)

- Given the attendance regularity, the prescribed drug is simply provided, as long as the patient has no doubts

The Pharmaceutical Consultation follow-up is a comprehensive examination, with the goal of collecting information regarding DDIs, knowledge of the patient regarding drug administration, relevant side-effects, and therapeutic adherence.

Current Situation at Pharmaceutical Ambulatory Care: Follow-Up Pharmaceutical Consultation



The existence of these three kinds of consultations is beneficial to the patient and the institution, as it takes advantage of each professional's strongest points and covers their weak points.

Current Situation at Pharmaceutical Ambulatory Care: Pharmaceutical Consultation - Internal Benchmarking

	1) DIAGNOSIS	2) EDUCATION		3) MONITORING AND ADJUSTMENTS		
		MEDICATION	NON-MEDICATION	APPOINTMENT REGULARITY	THERAPY ADHERENCE	DOSE ADJUSTMENT
DOCTOR	• The **initial diagnosis** is always performed by the **doctor**	• Education covers the **medication's most important characteristics** and expected adverse reactions	• Standard education	• **Regularity varies** with each patient's **clinical need** and the stage of their condition	• The patient's adherence is evaluated based on analytic and complementary **diagnosis and therapeutic methods**, through which **disease progression can be measured**	• The **doctor** always makes the **final decision** concerning **any changes** to the patient's therapy
PHARMACIST	• The **pharmacist** is capable of identifying cases in which the **prescription is not in accordance** with the doctor's diagnosis.	• **Complete education** regarding the **medication's intake and characteristics** (pharmacokinetic, pharmacodynamic and expected adverse reactions)	• Standard education	• **Regularity varies** with the established **frequency of medication distribution**. Appointments will be more frequent for new drugs, as they are less known/studied	• Patients' adherence is **monitored** through **pill counting**	• **Adjustments** are suggested when **toxicities are detected**, often as a result of DDIs and/or overdosing
NURSE	• The **nurse does not influence** the **initial diagnosis**	• Standard education	• More **detailed education** concerning what the patient should take into account in **daily care**	• Given to referenced patients **after the 1st medical appointment**, with a possibility of **future nursing appointments** according to each **patient's need**	• Adherence is **not monitored directly**, but the nurse attempts to identify **risk factors** which suggest bad adherence	• The nurse **does not act** over the **recommended dosage**

The existence of these three kinds of consultations is beneficial to the patient and the institution. Pharmaceutical Consultations add the most value in the Medication component of patient education and as an added control method for Therapy Adherence.

Current Situation at Pharmaceutical Ambulatory Care: Pharmaceutical Consultation - Internal Benchmarking

The main strong point of IPO's pharmaceutical consultations lies in optimizing the amount of time necessary to cover all essential subjects, when compared to the benchmark cases.

Current Situation at Pharmacy Ambulatory Care: Pharmaceutical Consultation - External Benchmarking

# of Pharmacists in outpatient care: 2-3	Patients/Hour = 21	Patients/Pharmacist = 90

IPO Scheduling and Service

Consultations are not scheduled	The 1st consultation tends to occur after the 1st medical appointment. The pharmacist is only made aware of a patient's need for a detailed consultation after their arrival at the pharmacy.
Consultations occur whenever outpatients come to pick up additional doses of the selected medicines	Subsequent consultations occur whenever outpatients come to pick up additional doses of drugs included in the program (currently ≈ once per month). These appointments are maintained throughout each patients' entire treatment.

IPO Consultation Procedure

Consultations can take between 15 to 20 minutes	Necessary time is optimized while covering all topics included in the benchmark institutions' P.C., apart from analysing outpatients' clinical records before each appointment.
Consultation is performed for a single drug	For now, P.C. occur only for Ibrutinib, chosen according to the following criteria: cytotoxicity; expensive price; high number of adverse effects and potential drug-drug interactions; being administered orally and continuously.

IPO Data Analysis

The main evaluated factor is therapeutic adherence	Therapeutic adherence is measured prospectively, by directly counting the number of leftover pills from the previous distribution. That number is then compared to what would have remained if the patient had perfectly followed the prescription.

At HGO, all P.C. after the first are scheduled. This institution successfully manages to perform P.C. while serving a high number of outpatients due in part to its strong back office support.

Current Situation at Pharmacy Ambulatory Care: Pharmaceutical Consultation - External Benchmarking

# of Pharmacists in outpatient care: 4 | **Patients/Hour = 25** | **Patients/Pharmacist = 63**

HGO Scheduling and Service

Scheduling for every consultation after the first

After the first P.C. every subsequent consultation is scheduled, in such a way that they become concentrated on certain days of the week. Patients also receive a phone call on a later date to ensure proper follow-up.

High level of back office support

Although there is a single pharmacist directly distributing medicine in a Front office position, the support of 3 other pharmacists makes it possible to address a daily inflow of 250 outpatients.

HGO Consultation Procedure

Consultations take between 15 to 40 minutes. Patients' clinical records are analysed beforehand.

The pharmacist examines each outpatient's clinical record for 30 minutes before the P.C. The first consultation will usually last 30-40 minutes, while subsequent visits take around 15 minutes.

Monthly calendars for drugs with complex (cyclical) prescriptions.

Pharmacists create and distribute monthly calendars for medicines meant to be taken cyclically. All relevant days are clearly marked on these calendars in order to ensure a proper dosage is taken.

HGO Data Analysis

The main evaluated factor is therapeutic adherence

Adherence is measured retrospectively: only the time between appointments and the number of pills given in the previous consultation are taken into account, there is no pill counting. This method saves time, although the records will be less precise in return.

The quantity of distributed pills may vary with a patients' adherence.

Patients with consistently bad records of therapeutic adherence (under 90%) are given a smaller amount of pills, corresponding to a shorter time period. This increases the number of times those patients will need to replenish their doses, which allows a tighter control.

At HESE, pharmaceutical consultations are only performed for injectable treatments, which implies a focus on the first consultation and in ensuring the patients' comprehension. Subsequent consultations are only performed when necessary.

Current Situation at Pharmacy Ambulatory Care: Pharmaceutical Consultation - External Benchmarking

# of Pharmacists in outpatient care: 3	Patients/Hour = 11	Patients/Pharmacist = 25

HESE Scheduling and Service

The scheduling of the first consultation is mandatory.

Patients must schedule a P.C. before they are allowed to withdraw their medication. They are informed of this procedure by their doctor at the time the treatment is prescribed at the institution.

Following consultations are subject to the patients' needs.

As a rule, subsequent consultations are not scheduled or mandatory. They occur only when requested by the patients themselves, or if the pharmacist deems them necessary.

HESE Consultation Procedure

P.C. can last between 25 to 60 minutes. Patients' clinical records are read beforehand.

Since the 1st P.C. tends to be the only one, the pharmacist analyses the clinical records and is flexible on the time spent with the patient according to their specific needs. As such, these can range from 25-60 minutes.

Performed only for injectable medication.

Consultations are exclusively implemented for oncological and HIV injectable drugs. One of the main factors leading to this decision was the danger in applying these injections at home, which patients must often do by themselves.

HESE Data Analysis

The main evaluated factor is therapeutic education.

Given the need to ensure patients understand the injecting process and the drug itself entirely, a follow-up phone call is made sometime after the appointment. This call also aids in detecting early side effects the patient might have experienced in the meantime.

AGENDA

AGENDA

5 Ibrutinib Pharmaceutical Consultation

i. Data Processing
ii. First-line Maintenance Analysis
iii. DDI and Dosage Adjustment Analysis

In order to calculate the outcomes of the Ibrutinib P.C. pilot-project, two studies focused on First Line Maintenance and Dosage Adjustments were performed.

Ibrutinib Pharmaceutical Consultation: Data Processing

In order to perform the aforementioned analysis, it was necessary to select a medicine upon which the initial investigation would be focused. The drug chosen for this end was **Ibrutinib.**

Why Ibrutinib

Ibrutinib was already in use in the pharmaceutical consultation pilot-study developed by the pharmacy's ambulatory care unit at IPO, which made it easy to collect data pertaining to scenarios **with** pharmaceutical consultations. The goal of this analysis is to grant IPO the necessary tools to evaluate the financial and economic viability of the P.C. and to make it possible to estimate the monetary incentives for expanding the consultations to other drugs.

First Line Maintenance Analysis

Defining the Analysis Model → Gathering patient data and defining therapy lines → Calculating T.R.R: and building Markov chains → Calculating the costs (total and per patient) → Incremental cost analysis → Summarizing and calculating financial indicators

DDI and Dosage Adjustment Analysis

Identifying interventions performed due to P.C. → Clinically significant drug-drug interactions (DDIs) → Identifying cost savings resulting from P.C. → Defining a model to estimate future savings → Summarizing all collected data

The added economic value of pharmaceutical consultations to IPO will be estimated by analysing and quantifying their impact on the values predicted by the disease progression models of the studied drugs.

Ibrutinib Pharmaceutical Consultation: Data Processing

Disease Progression Models

These models represent a disease's natural progression quantitatively, based on mathematical functions which incorporate characteristic bio-markers. These are usually associated to pharmacodynamic models which intend to assess how the applied drugs might influence disease progression.

Markov Chains for Cost Optimization

Markov chains are utilized in order to quantify costs and measure risks associated to each therapeutic regimen, taking into account a finite number of events which may occur along patients' treatment cycles. In this way, the model takes the shape of a tree diagram, on which are represented the existing scenarios (maintaining 1st line treatment or advancing to 2nd line) along pre-defined time periods, along with the respective probability of each scenario occurring. In the case of oncology treatments, **moving to the 2nd line** usually occurs when the patient either experiences **excessive toxicities with the 1st line treatment** or if and when this treatment **stops having the necessary effectiveness** in that patient's situation.

Net Present Value (NPV) Analysis

Present value of future predicted economic benefits (cash flows), taking into account the incurred costs.

$$NPV = \sum \frac{(CF)}{(1+r)^n}$$

CF – Cash Flows

R- discount rate*

n- period

Quantification of Cost Optimization (Cost-Effectiveness)

Analysing the cost-benefit relationship by measuring the variation of these two components. This is a percentual (i.e. not absolute) indicator, which simplifies the comparison across different scenarios.

$$Cost - Effectiveness = \frac{(\Delta\ costs)}{(\Delta\ benefits)}$$

Δ – variation

*Reference discount rate determined by Banco de Portugal

Data collection for Ibrutinib patients was exhaustive. The variation in patients' quality of life was not measured due to the ambiguity of this metric.

Ibrutinib Pharmaceutical Consultation: Data Processing

Data Processing

Data was collected from all patients who took Ibrutinib during the last 2 years (n = 62), related to the following points:

- Ibrutinib first prescription date
- Dates of all Ibrutinib P.C. performed for each patient, standardizing each date in order to allow direct comparison between patients
- Ibrutinib final prescription date, when applicable
- All dosage alterations, making a distinction between those that occurred due to medical interventions and those that only occurred as a result of pharmaceutical intervention
- Variation in the number of pills taken per day as a result of each intervention
- Therapeutic adherence rate calculated during the consultations, when possible
- The total variation upon patients' quality of life was not taken into account due to a lack of consensus on how its value should be measured, pertaining to economic issues and social pressure

1117116				
Date	Maintained 1st line	Dosage Adjustment	Variation	Adherence
13/03/2018				
03/04/2018	1	0	0	100
24/04/2018	1	0	0	100
15/05/2018	1	0	0	90
05/06/2018	1	0	0	NA
03/07/2018	1	0	0	NA
31/07/2018	1	0	0	101.2
23/08/2018	1	0	0	155.1
25/09/2018	1	0	0	90.9

1117116				
Date	Maintained 1st line	Dosage Adjustment	Variation	Adherence
Date 1				
Date 2	1	0	0	100
Date 3	1	0	0	100
Date 4	1	0	0	90
Date 5	1	0	0	NA
Date 6	1	0	0	NA
Date 7	1	0	0	101.2
Date 8	1	0	0	155.1
Date 9	1	0	0	90.9

Ibrutinib Pharmaceutical Consultation: Data Processing

Exclusion Criteria

In order to ensure an objective, unbiased analysis, a total of 25 patients were excluded from this study (**Annex 3**), due to the following criteria:

- The patient was only included in the P.C. program several months after beginning treatment with Ibrutinib (n = 7)

These patients were excluded as measuring the impact of P.C. throughout the first months after beginning the treatment was considered essential. These patients were only included after this critical period, and in some cases over a year after beginning Ibrutinib treatment, for various reasons.

- Insufficient patient registry data - less than two entries (n = 17)

In these cases it is not possible to create a trustworthy record of a patient's history.

- The patient was unable to make his/her way to IPO in order to pick up his/her prescription, in which case they were mostly delivered by firemen (n = 1)

Since the P.C. takes action through direct contact and patient education, it cannot be performed when the patient is not personally present for at least the majority of pick-up dates

A detailed demographic overview of the 37 included patients is available in **Annex 4.**

1037913				
Date	Maintained 1st line	Dosage Adjustment	Variation	Adherence
21/07/2015				
07/01/2016	1	0	0	100
08/02/2016	1	0	0	100
07/03/2016	1	0	0	100
04/04/2016	1	0	0	100
18/10/2016	1	0	0	100
15/11/2016	1	0	0	100

Data relating to each patient's first 12 months of treatment was processed. The two main pathologies associated with Ibrutinib will need to be considered separately.

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

Throughout the initial study, which only included Ibrutinib, data pertaining to 24 months was collected, with a final sample of 37 outpatients.

Analysis of the number of monthly outpatients across the first 12 months

Date 1	Date 2	Date 3	Date 4	Date 5	Date 6	Date 7	Date 8	Date 9	Date 10	Date 11	Date 12
37	37	35	35	30	28	25	19	16	13	11	7

All normalized Ibrutinib entries since June 2016 were registered. Throughout the first 12 dates there is a noticeable gradual reduction in the number of patients for two motives:

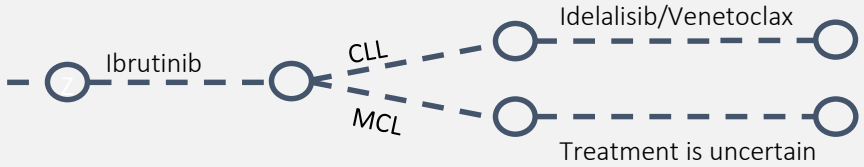
- Entry of new patients in the last year who still only have records for a few dates
- Some patients passed away

Treatment of the Number of Patients by Date

Although, throughout the dates, there is a reduction in the number of patients, by comparing those who are still following the analysed treatment line at the end of each period against those who were present at the beginning of the corresponding period, it is possible to obtain the necessary percentages to build the Markov Chains.
Cost savings calculations will only take into account patients who, in each period, are still within their first 12 months of treatment.

Differentiated Study of Two Pathologies

Ibrutinib is mainly used to treat two pathologies: Chronic Lymphocytic Leukaemia (CLL) and Mantle Cell Lymphoma (MCL). These are associated with very different progression models and carry different subsequent treatment options. In the case of LMC, post-Ibrutinib treatment is still uncertain and decided on a case-by-case basis. [1]



1. Jacobson, C. A., MD. (2018, February 21). Beyond Ibrutinib for Mantle Cell Lymphoma. Retrieved from http://www.hematology.org/Thehematologist/Diffusion/8303.aspx

Ibrutinib is a high-cost drug, with a high number of possible DDIs and side effects. The subsequent treatments for LLC are equally expensive and also significantly toxic to patients' health.

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

In the case of CLL, it is necessary to consider the following recommended treatment lines which, unlike for MCL, are defined more objectively:

Ibrutinib – 1st line

Cost per 28 days: 5438€

- Taken daily, in initial doses of 420mg – 3 pills
- Relevant DDIs which can imply the need for reducing dosage
- High number of adverse reactions, some of which can reach grades 3 and 4, which imply dosage reduction

Idelalisib – 2nd line

Cost per 28 days: 3311€

- Taken daily, in initial doses of 300mg – 2 pills
- High number of adverse reactions, some of which can reach grades 3 and 4, which imply dosage reduction
- Used as the 2nd line treatment for Ibrutinib, but due to its high toxicity it is sometimes passed over in favour of other medication with lower effect and toxicity
- Must be taken in conjunction with an IV medication (Rituximab) weekly for the first 2 months of treatment, which adds 3588€ to the monthly cost during this period*

Venetoclax – new 2nd line

Cost per 28 days: 1st month - 1377€

Subsequent months - 5956€

- Taken daily, in a dosage which increases gradually week after week, stabilizing after the 5th week
- High number of adverse reactions, some of which can reach grades 3 and 4, which imply dosage reduction
- Must be taken in conjunction with an IV medication (Rituximab) for the first 6 months of treatment, which adds 897€ to the cost of the first month and 1173€ to the monthly cost of the following 5 months*
- Potentially very toxic at the beginning of treatment, but allows a better quality of life and treatment outcomes for the patient in the long-run

*Rituximab cost estimated for a patient measuring 1.65m and weighing 70kg

The construction of Markov Chains allows for a graphic representation of the progression models of the disease and the temporal evolution of the patients between treatment lines. In these, the probability of a patient remaining in the current treatment line or transitioning to the following is estimated for each period.

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

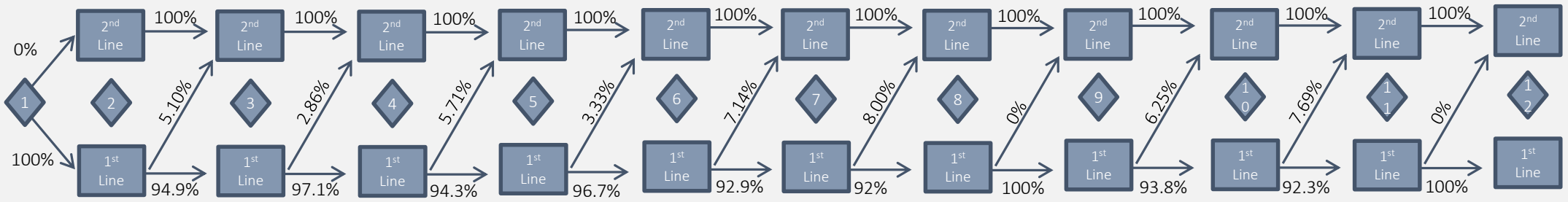
Within the Markov Chains, for each period (represented by a lozenge) there are two options of progression:

1. As long as they are in the first line of treatment, patients can either stay on this line or progress to the subsequent one
2. Once on the second line of treatment, patients tend to remain on it until they pass away; they can however, in exceptional cases, return to the first line or switch to an entirely different medication later on (although such cases were not observed within the analysed period, hence the probabilities in the upper row of the chains are always equal to 100%).

To proceed to the construction of these chains, it is necessary to compute the Treatment Retention Rates, which represent the probability of, by the end of each period, a patient who began on a specific line remaining on that line. This way, the ideal TRR for the first line is 100%, as such reveals that all patients reacted, in clinical terms, effectively to the medicine and did not experience any toxicities that demanded a transition to a subsequent line.

$$\text{TRR} = \frac{Number\ of\ patients\ within\ the\ considered\ line\ by\ the\ \boldsymbol{end}\ of\ the\ period}{Number\ of\ patients\ within\ the\ considered\ line\ at\ the\ \boldsymbol{start}\ of\ the\ period}$$

Markov Chain **WITH** Pharmaceutical Care (example CLL)



Based on data supplied by the Ambulatory Service of IPO's Pharmacy

Through the transformation of the directly built Markov Chains into chains that assume the average of the probabilities registered in the first 12 months of treatment, it is possible to obtain a systematised progression model that allows a simplified manipulation and comprehension of the data. This conversion does not have a significant financial impact.

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

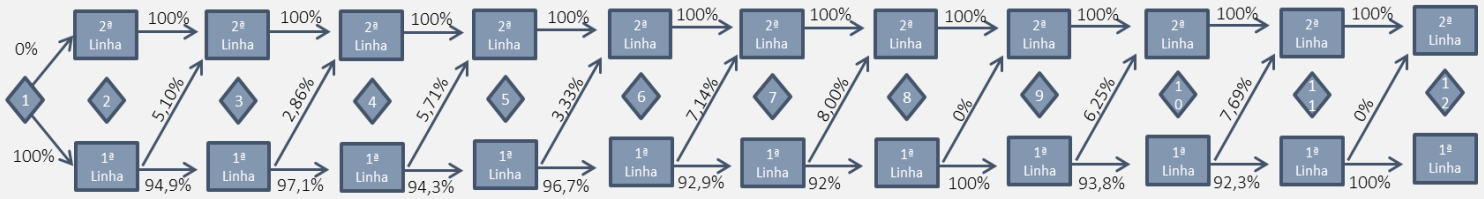
Aiming to systematise the analysis and enable a more methodical evaluation of the data and results, the chains representing disease progression were recalculated in order to assume the average value of the Treatment Retention Rates. The validation of this method allows the simplification of future predictions as, for each treatment line, there will be a need to estimate annual expenses considering the number of new patients.

$$\overline{\text{TRR}} = \frac{\Sigma\ (\text{TRR in the first 12 months})}{12}$$

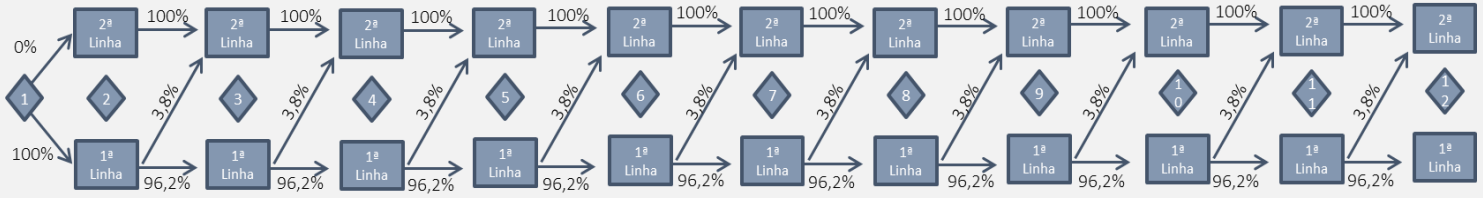
This way, the simplified model assumes:

- The 12-month average of the TRR
- The monthly cost of the different lines of treatment for the pathology in study
- The yearly number of new patients in each line

Markov Chain **WITH** Pharmaceutical care **DIRECTLY BUILT**



Markov Chain **WITH** Pharmaceutical care **SYSTEMATISED**



During the conversion process of the **directly built chains** to the **systematised model**, a **financial impact analysis** was performed in order to confirm whether or not this model was a **reliable replication**.

To that end, and empirical study was performed, in which the Markov Chain was transformed to assume the **average of the TRR** for both the maintenance in the first line treatment and for the transition to the second. The values for the **number of new patients** and **prices of medication** were kept constant for their respective treatment lines.

Afterwards, the **variation in the value of expenses** for each method was recorded for both methods. The annual variation was **below 1%.** Thus, for the subsequent analysis, the **average of the TRRs was assumed**.

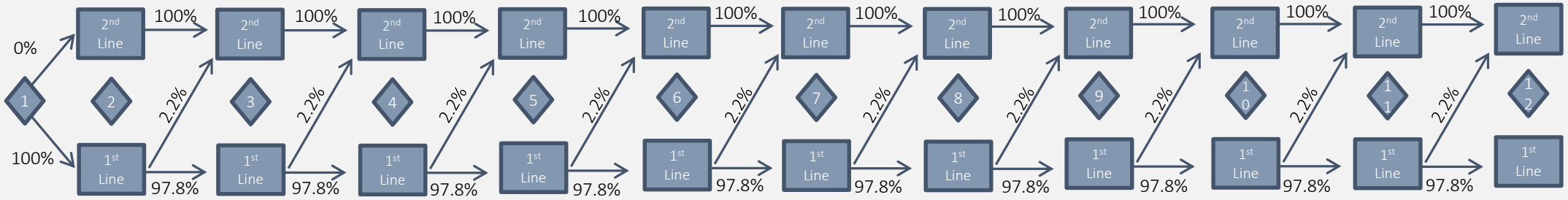
Based on data supplied by the Ambulatory Service of IPO's Pharmacy

Considering that Ibrutinib is used to treat two different pathologies, it is necessary to perform a differentiated analysis of their variables as they will influence differently the cost reduction potential. In the case of CLL it is possible to calculate the savings obtained due to the existence of a clear 2nd line treatment.

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

As Ibrutinib is essentially applied to the treatment of two pathologies, the study of the individual progression models was executed through the construction of two separate, systemized Markov Chains. It is important to notice that these pathologies imply a different daily pill dosage, which leads to different values for the monthly expenses per patient.

Markov Chain **WITH** Pharmaceutical care **L.L.C**



Data Summary

Average monthly number of patients (Currently)	Average annual number of new patients	Average TRR	Number of pills (daily)	Average monthly cost	Second Line	Monthly Cost
16.4	8	97.76%	3	5,438.16€	Venetoclax	5,955.99€*

*Observations::

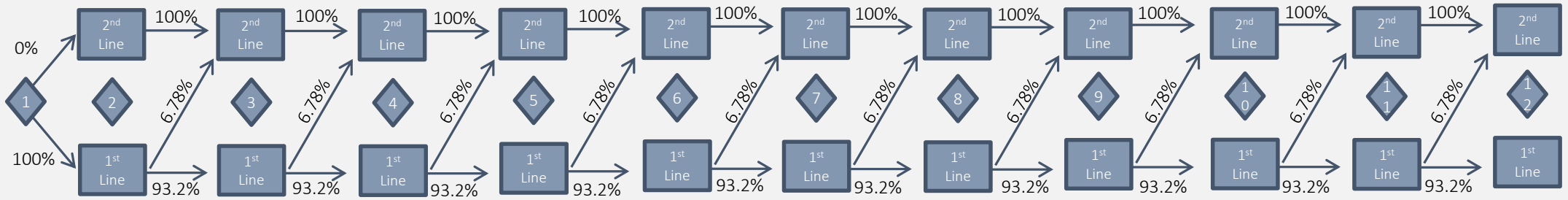
- Cost of the first month: 1,377.32€
- During the first 6 months, Venetoclax needs to be taken with Rituximab, with represents an increase in monthly costs of 1173€

Based on data supplied by the Ambulatory Service of IPO's Pharmacy

In the MCL case, the savings obtained with the reduction of transitions to the second line of treatment cannot be performed in a reliable way. Notwithstanding, the implementation of pharmaceutical consultations is beneficial to these patients.

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

Markov Chain **WITH** Pharmaceutical Consultation **MCL**



Data Summary

Average monthly number of patients (Currently)	Average annual number of new patients	Average TRR	Number of pills (daily)	Average monthly cost	Second Line	Monthly Cost
7.6	8	93.2%	4	7,250.00€	*	*

Despite the fact that Ibrutinib for Mantle Cell Lymphoma doesn't have a clear and well-defined subsequent line of treatment, as the following medicine needs to be evaluated individually for each patient, the analysis of its TRR was still performed for the following reasons:

- The verified TRR, compared with the one from LLC, is relatively lower, hence it is possible that there may be a larger margin for improvement for these patients.
- The analysis of the evolution of the TRR can be utilized as a measure to control the effectiveness of pharmaceutical consultations. These will be implemented for this therapeutic line, as there are further economical and clinical benefits recorded, that will be explained further on during the analysis of drug-drug interactions.

The analysis of the cost reduction through the maintenance in the 1st line underlies a mathematical model that continuously analyses the progression of the disease in the patients during their first 12 months of treatment.

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

$$\boldsymbol{Expenses\ (12\ Months) = \sum nr\ new\ patients * monthly\ costs\ (t)}$$

Calculation of monthly costs

Inputs: $C_1 = Cost\ in\ line\ 1$ $C_2 = Cost\ in\ line\ 2$

$P_0 = \boldsymbol{without\ consultation}, TRR\ of\ transitioning\ to\ line\ 2 \Rightarrow [1 - P_0] = \boldsymbol{without\ consultation}, TRR\ of\ \boldsymbol{not}\ transitioning\ to\ line\ 2$

$P_i = \boldsymbol{with\ consultation}, TRR\ of transitioning\ to\ line\ 2 \Rightarrow [1 - P_i] = \boldsymbol{with\ consultation}, TRR\ of\ \boldsymbol{not}\ transitioningto\ line\ 2$

Example of calculation of the individual monthly cost, under the pharmaceutical consultation scenario:

➢ Date 1

$$Cost\ t_1 = P_i \times C_2 + (1 - P_i) \times C_1$$

TRR of **with consultation** *transitioning to line 2× Cost of line 2+ TRR of* **with consultation** *not transitioning to line 2 × Cost of line 1*

➢ Date 2

$$Cost\ t_2 = P_i \times C_2 + (1 - P_i) \times [P_i \times C_2 + (1 - P_i)C_1]$$

TRR of **with consultation** *transitioning to line 2× Cost of line 2+ TRR of* **with consultation** *not transitioning to line 2 ×*

- *Of those that transitioned to line 2, the cost of staying in line 2*
- *Of those that stayed in line 1, the cost of staying in line 1*

➢ Date 3

$$Cost\ t_3 = P_i \times C_2 + (1 - P_i) \times \left[P_i \times C_2 + (1 - P_i) \times [P_i \times C_2 + (1 - P_i)C_1]\right]$$

TRR of **with consultation** *transitioning to line 2× Cost of line 2+ TRR of* **with consultation** *not transitioning to line 2 ×*

- *Of those that transitioned to line 2 in t2,, the cost of staying in line 2 for a month*
- *Of those that transitioned to line 2 in t1, the cost of staying in line 2 for two months*
- *Of those that stayed in line 1, the cost of staying in line 1 for three months*

Due to the lack of need to proceed to an initial investment for this project, the cost study merely concerns the analysis of the opportunity cost of the pharmacists' time. As the pilot project included a reduced number of patients, the monthly time increase was moderated and a reorganization of the activities was possible, which led to a null opportunity cost.

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

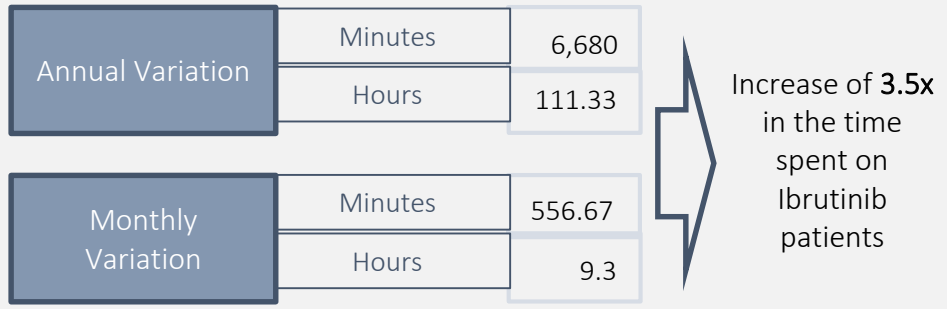
The implementation of the pharmaceutical consultations leads to an increase in the time spent assisting patients, which can entail further costs. In the context of the study of cost increment study, an analysis of the opportunity cost of the pharmacists' time was performed. The opportunity cost analysis involves the calculation of the value associated to the best unchosen alternative.

Scenario **without** pharmaceutical consultation Ibrutinib (LLC + LM)

Type of Care	Average Duration	Number of Consultations	Total Annual Time (Min.)	Total Monthly Time (Min.)
1st Consultation	10 min	23	230	19.17
Prescription Alterations	5 min	15	75	6.25
Simple Distribution	3 min	525	1,575	131.25
Total	-	563	1,880	156.67

Scenario **with** pharmaceutical consultation Ibrutinib (LLC + LM)

Type of Care	Average Duration	Number of Consultations	Total Annual Time (Min.)	Total Monthly Time (Min.)
1st Consultation	20 min	23	460	38.33
Subsequent Consultation	15 min	540	8,100	675
Total	-	563	8,560	713.33



Although the implementation of this type of care requires an increase in the necessary time to assist patients, the reorganization of activities allowed for the maximization of the efficiency of the pharmacy. Thus the **opportunity cost** observed was approximately **null.**

The application of the pharmaceutical consultations only over the first 12 months after starting treatment aims to optimise the installed capacity of the ambulatory service, as this time can now be allocated to other medicines

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

Scenario **with** pharmaceutical consultations Ibrutinib **patients on the first 12 months**

Type of Care	Average Duration	Number of Consultations	Total Annual Time (Min.)	Total Monthly Time (Min.)
1st Consultation	20 min	8	160	13.33
Subsequent Consultation	15 min	88	1,132	110
Prescription Alterations	5 min	15	75	6.25
Withdraw	3 min	452	1,356	113
Total	-	563	2,911	242.58

Scenario **without** pharmaceutical consultations Ibrutinib

Total	-	563	1880	156.67

Annual Variation	Minutes	1,031
	Hours	17.18
Monthly Variation	Minutes	85.92
	Hours	1.43

1.55x increase on the time spent, in comparation to the initial scenario

Scenario **with** pharmaceutical consultations Ibrutinib **for all patients**

Total	-	563	8560	713.33

Annual Variation	Minutes	-5,649
	Hours	-94.15
Monthly Variation	Minutes	-470.75
	Hours	-7.85

2.94x decrease of on the time spent, in comparison to the current paradigm

- ✓ Considering that the pharmaceutical consultation will only be adopted for patients that are in their first 12 months of prescription, it is necessary to verify in which way this adjustment will affect the ambulatory activity.
- ✓ Hence, a comparative analysis was performed, in which a third scenario was created. In this, the **patients in the first 12 months** where considered in the scenario **with** consultations and the **remaining** in the scenario **without** consultations.
- ✓ This change leads to a monthly reduction of **7.85 hours**. Such implies a significantly smaller increment to the necessary time to serve the patients in this program (only 1.55x greater, compared to the current scenario which is 3.55x superior). This time can be used to apply this care to other pathologies.

The level of savings generated, the net present value and the cost-effectiveness ratio are three indicators that make it possible to objectively analyse the economic benefits generated from the pharmaceutical consultation

Ibrutinib Pharmaceutical Consultation: First-line Maintenance Analysis

Once computed the monthly and annual costs in the two scenarios, with and without pharmaceutical care, and the costs associated with the implementation of this service, it is possible to compute several financial and economical indicators.

1.Savings Generated, net of costs (Absolute Indicator, in euros)

Merely represents **the difference between the cost incurred** in the two scenarios. By knowing the savings generated, it is possible to know **the maximum expenses** that can be incurred, while ensuring the pharmacy consultations are still **financially viable**.

2. Net Present Value (Absolute Indicator, in euros)

Represents the effective savings verified over the 12-month period after the pharmaceutical consultation implementation. This means computing the difference between the present value of savings generated and the value of costs incurred during the process. So, as long as the value of this indicator is positive, effective monetary savings are occurring for IPO. Additionally, this indicator makes it possible to compare different scenarios that require different levels of investment, and understand which ones generate the greater economic benefits in terms of euros saved.

$$\text{NPV} = \sum \frac{(E.C)}{(1+r)^n}$$

3. Cost-Effectiveness (Relative Indicator – costs incurred for each euro saved)

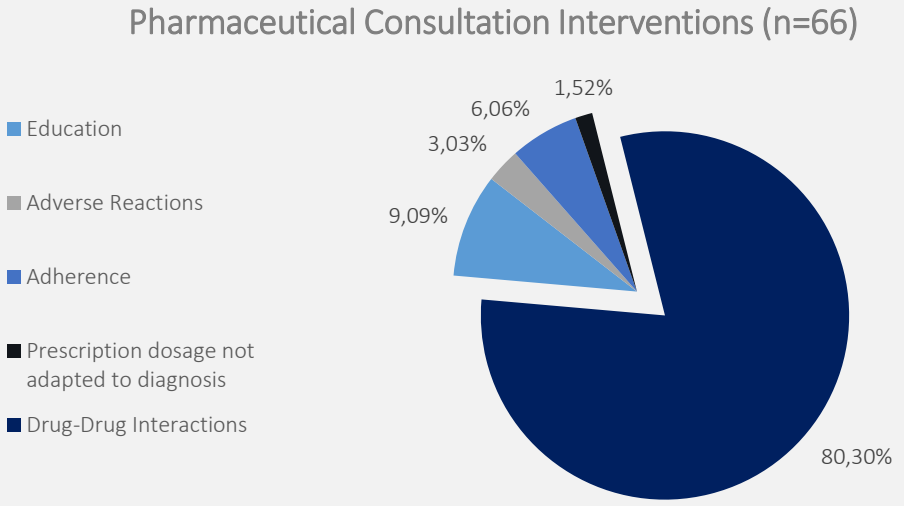
Indicates the **economic and financial efficiency** by **comparing the savings** verified **with the costs** that had to be incurred in **order to generate 1 additional euro of savings**. Thus, the lower this value is, the better the indicator and the scenario, as lower costs had to be sustained to generate the same level of savings. When the value of this ratio is 1 we are at the break-even point, in which costs equal benefits. Anytime this value exceeds 1, the costs have surpassed the benefits, thus indicating the financial situation is unfavourable.

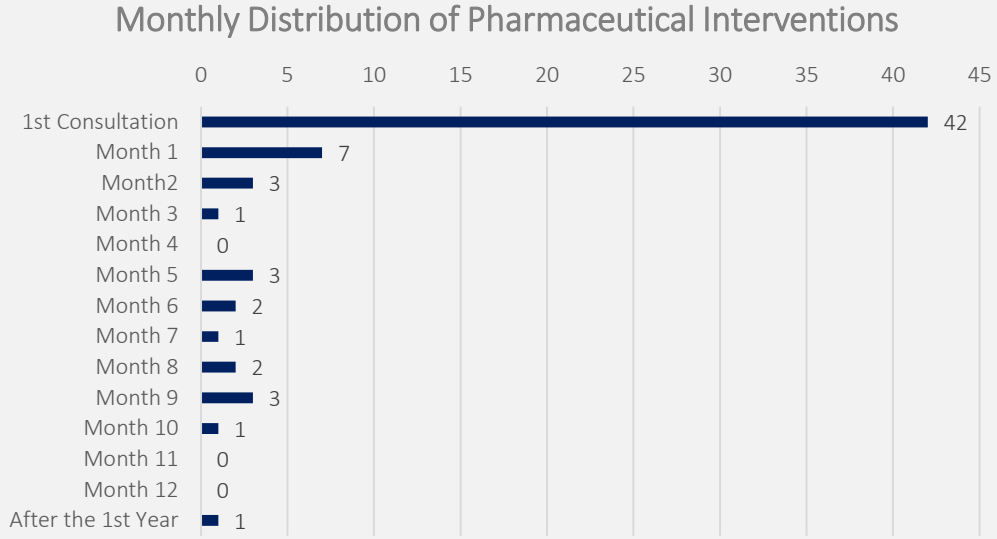
$$\boldsymbol{Cost - Effectiveness} -= \frac{(\Delta\, Costs)}{(\Delta\, Benefits)}$$

Cost-Effectiveness, by being a **relative indicator**, allows for a greater comparison between different medicines and lines of treatment whose absolute savings values and associated costs diverge significantly. In this way, it can be used as a tool to assist the decision-making process under different scenarios.

The need for pharmaceutical interventions as a result of P.C. is highest during the first month after beginning treatment with Ibrutinib. 80% of these interventions were due to detected DDIs, which will have contributed to an improvement in these patients' clinical outcomes.

Ibrutinib Pharmaceutical Consultation: DDI and Dosage Adjustment Analysis

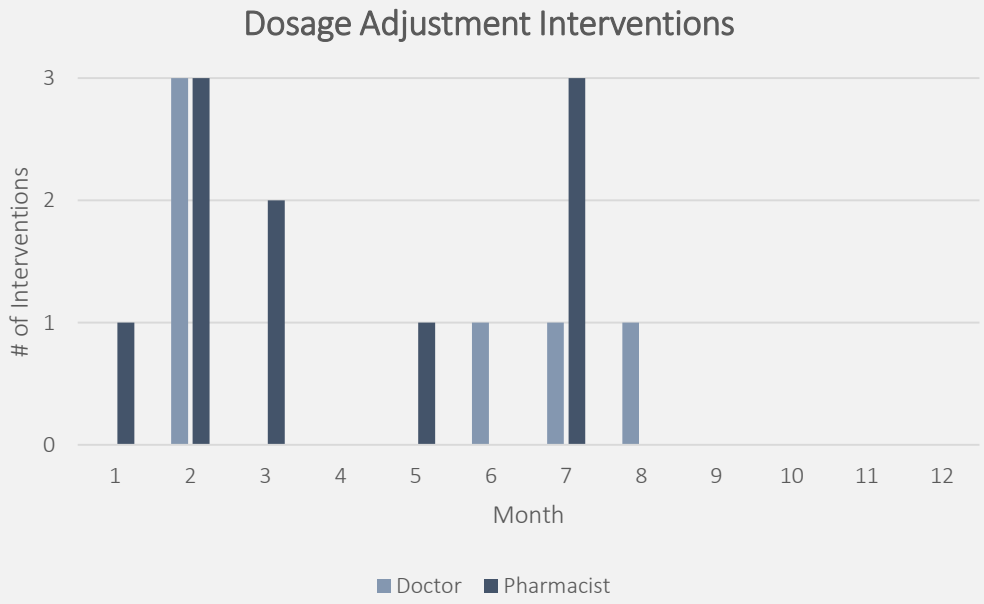




- Considering patients who began attending P.C. throughout a 24-month period (01/06/2016-31/05/2018), a total of **66 pharmaceutical** interventions were performed on 40 of the 62 outpatients - **65% -** seen during this time.
- These interventions can be split into 5 categories: **Education; Adverse reactions; Adherence; Dosage Not Concordant with Diagnosis, and Drug-Drug Interactions.** Over **80%** of the interventions performed were due to **dangerous drug interactions** detected by the pharmacist.
- **Over 60%** of all interventions occurred at the time of each patient's **1st consultation,** and they became progressively **less frequent after the 1st month** of care. **After one year** of regular appointments, the **need of interventions** was almost **non-existent.**
- Through these interventions, particularly due to the number of DDIs that would have gone undetected otherwise, these patients were **exposed to a lower toxicity**, which could have contributed to prolong the time they were able to keep following this line of treatment.

The study of interventions which imply dosage adjustments performed by doctors and pharmacists suggests that these generally occur within the first 12 months of treatment, with pharmaceutical detection happening on average within the first 4 months in patients taking Ibrutinib.

Ibrutinib Pharmaceutical Consultation: DDI and Dosage Adjustment Analysis



Total number of Interventions	Doctors	6
	Pharmacists	10
Average Time of Intervention (in months)	Pharmacists	3,9

Throughout a 24 month period, the following graph registers which medical and pharmaceutical interventions implied a dose adjustment. All of these cases occurred within the first 12 months after the patient had begun taking Ibrutinib.

- A total of **10 dosage reductions** were performed due to the pharmacists' advice, **9** of which were related to **detected DDIs** and **1** due to the patient's **prescription not being adapted to their diagnosis**. Of these interventions, 6 directly reduced the dosage of Ibrutinib, while 4 impacted other medication taken by those patients.

- **Medical adjustments** were mostly related to the **patients' response to therapy,** as opposed to the **detection of interactions** with other drugs.

It is also worth noting that **pharmaceutical interventions occur on average within the first 4 months**, which suggests the first periods of treatment are those that require a more exhaustive analysis of the patients' condition.

Pharmaceutical interventions which took place due to DDIs led to cost saving of 46.000€ across 24 months, which reduced Ibrutinib expenses by 3.63%. 83% of these interventions occurred in CLL patients.

Ibrutinib Pharmaceutical Consultation: DDI and Dosage Adjustment Analysis

Record of Interventions with Direct Financial Impact

MONTH	Number of interventions	Daily pill variation	Cause	Duration	Cost savings	Pathology
1	1	-2	DDI	6 months	11733€	CLL
2	3	-1	Dosage not adapted to diagnosis	5 months	11133€	CLL
		-1	DDI	6 months	13000€	CLL
		-2	DDI	1 week	933€	MCL
3	0	0				
4	0	0				
5	1	-2	DDI	2 months	7333€	CLL
6	0	0				
7	1	-1	DDI	1 month	1942€	CLL
8	0	0				

Of all interventions, **6 had a direct financial impact,** leading to **cost savings of 46.074€,** which represented **3.63% of Ibrutinib expenses in 2017,** distributed by the pharmacy across 12 months (assuming the price of the last 24 months).

It is worth noting that **80%** of these savings occurred within the **first two months.** This reinforces the need of having a pharmacist analyse potential DDIs in order to minimize not only costs but also dangers to patients' wellbeing resulting from these interactions.

Within these **6 interventions, 5 (83%) occurred in CLL patients** and represented **97% of total cost savings.**

The **classification** of the DDIs pertaining to their severity can be found in annex XXX

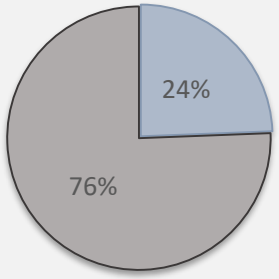
The observed cost savings related to DDIs as a result of consultations lead to estimated annual savings of 17.000€ for Ibrutinib.

Ibrutinib Pharmaceutical Consultation: DDI and Dosage Adjustment Analysis

Since the necessary inputs to estimate these cost savings for the scenario in which the P.C. will only be applied to patients within their first year of medication had already been collected, it was possible to perform this analysis for each of the two main Ibrutinib pathologies.

$$Yearly\ Savings = Number\ of\ patients\ covered\ in\ P.C. \times Avg\ \%\ of\ interventions \times Avg\ value\ of\ savings$$

Drug-Drug Interactions and Dosage Alterations CLL

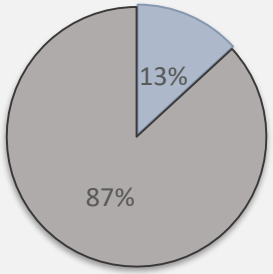


Average number of patients	16,4
Patients with interventions	4
Number of interventions	5

Number of new patients	8
Percentage of patients with interventions	24%
Average cost savings of interventions per patient	8.360€

- Yearly Savings – 16.051,20€
- Monthly Savings– 1.337,60€

Drug-Drug Interactions and Dosage Alterations MCL



Average number of patients	7,6
Patients with interventions	1
Number of interventions	1

Percentage of patients with interventions	13%
Average cost savings of interventions per patient	933€

- Yearly Savings – 933,00€
- Monthly Savings – 77,75€

AGENDA

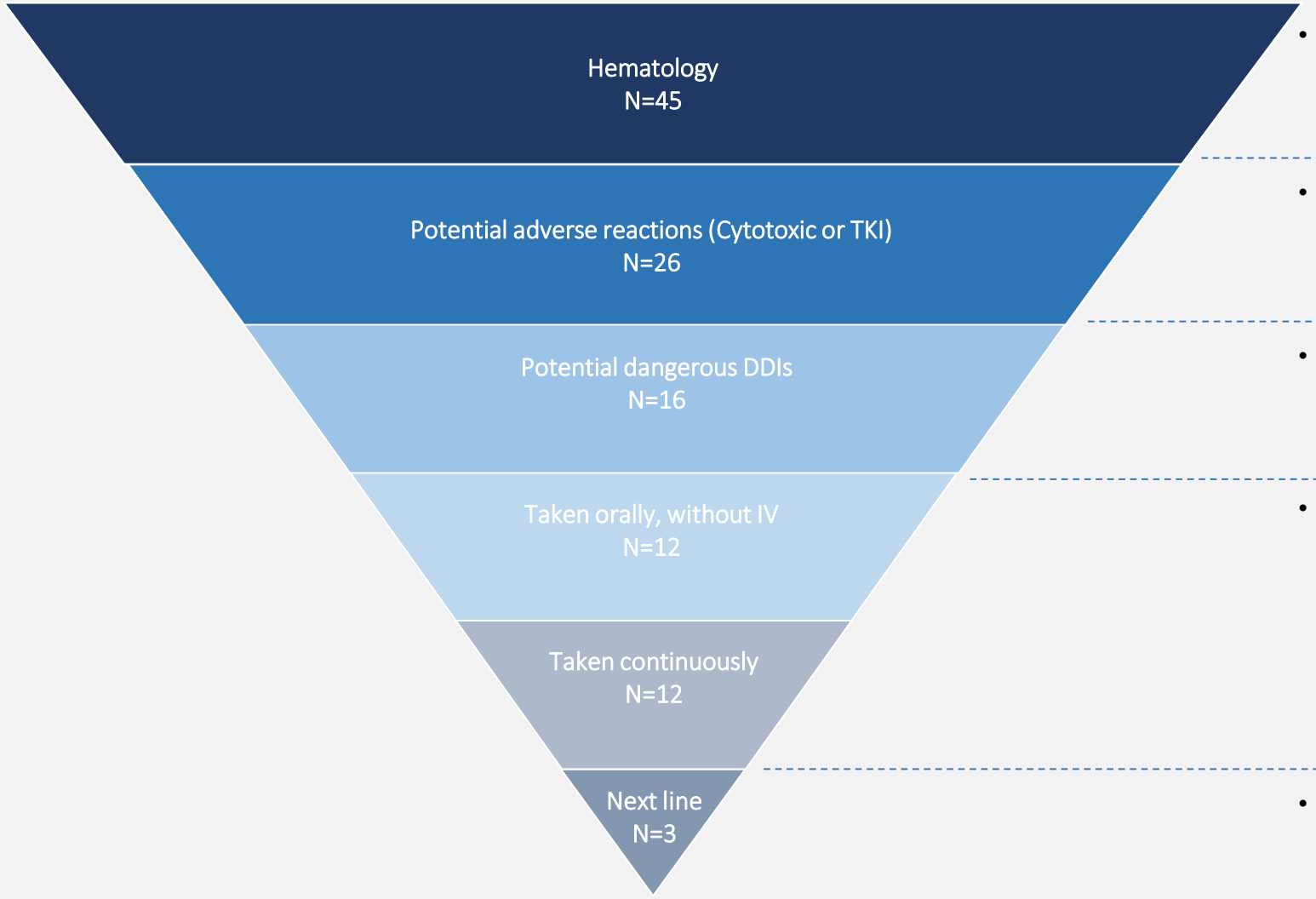
AGENDA

6 Pharmaceutical Consultation Expansion

i. Short-term expansion
ii. Long-term expansion

From the 122 drugs distributed at IPO's ambulatory care, 3 were identified as carrying the highest priority for inclusion in P.C.

Pharmaceutical Consultation Expansion: Short-term expansion



- Although only 12.56% of outpatients take Hematology medication, the average cost of the drugs used by these patients' is 4.4x times higher than the average for IPO patients
- Drugs with the potential to cause grade 3 or above reactions often imply serious danger to a patient's wellbeing
- The benefits of including drugs with potential dangerous DDIs in P.C. include not only improvements to patients' wellbeing but also financial cost savings
- Patients taking drugs which are not administered orally and continuously have, in general, a greater medical care, which makes these medicines a less immediate priority for inclusion in P.C.
- Medication used in later treatment lines is, sometimes, substantially more expensive than the previous treatment line

Drugs with the potential to cause grade 3 or above reactions often imply serious danger to a patient's wellbeing.

Pharmaceutical Consultation Expansion: Short-term expansion

≥10%

Between 1% and 10%

Between 0.1% and 1%

Frequency (All grades)	Adverse reactions	All Grades (%)	Grade ≥ 3 (%)
Very common	Pneumonia*#	16	10
	Upper respiratory tract infection	19	1
	Sinusitis*	11	1
	Skin infection*	10	3
Common	Sepsis*#	4	4
	Urinary tract infection	9	2
Uncommon	Hepatitis B reactivation@	< 1	< 1

Classification of adverse reactions:

According to the Common Terminology Criteria for Adverse Events (CTCAE) [1], the danger level of adverse reactions which may occur due to a given medication is classified into 5 categories: **Grade 1** - Mild; **Grade 2 –** Moderate; **Grade 3 –** Severe or medically significant; **Grade 4 –** Life-threatening consequences; **Grade 5** – Death related to the adverse reaction. As they represent a serious threat to patients' wellbeing, the probability of reactions of Grade 3 or higher are also registered separately. These events are also classified according to their likelihood of occurring , from **Very common –** affect more than 10% of patients, to **Uncommon –** affects between 0.1% to 1% of patients.

Incidence in Oncology

Given the complexity and toxicity of chemotherapeutic treatments, the patients who take them are highly susceptible to adverse reactions. A prospective study performed by the Pharmacology Department of the Lady Hardinge Medical College in New Deli attempted to measure the **number of adverse reactions** in a sample of **1008 patients** from **15 oncological pathologies** throughout a **2-year period.** [2]

Throughout the study, a total of **591 adverse** reactions were observed, corresponding to an incidence of **58.6%.** Among these cases, **49% could have been prevented** and **12.9%** were considered serious (implied hospitalization and/or threatened the patients' lives).

Sources:

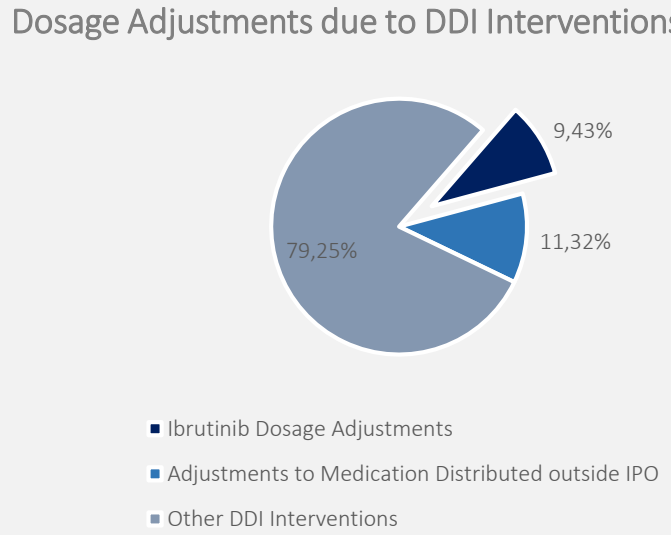
Summary of Product Characteristics Ibrutinib – European Medicines Agency

[1] Common Terminology Criteria for Adverse Events v5.0 (CTCAE) ." (2017, November 27). CTEP

[2] Chopra, Deepti, et al. (2016, March). Chemotherapy-Induced Adverse Drug Reactions in Oncology Patients: A Prospective Observational Survey.

The benefits of including drugs with potential dangerous DDIs in P.C. include not only improvements to patients' wellbeing but also financial cost savings.

Pharmaceutical Consultation Expansion: Short-term expansion



DDI Classification	Description
Major	Highly clinically significant, the risk of the interaction outweighs the benefit.
Moderate	Moderately clinically significant, use it only under special circumstances.
Minor	Minimally clinically significant, assess risk and consider an alternative drug

- Certain oncological medicines have a wide range of dangerous DDIs with other drugs, as is the case with Ibrutinib.
- Within the P.C. a total of 53 interventions were performed over DDIs. These can have significant consequences to patients' wellbeing by reducing their exposure to unnecessary toxicities, recommending for example a wider time period in between taking certain drugs at the same time as Ibrutinib.
- Within these interventions, the most crucial are those which imply the patient reducing and/or interrupting the intake of the main medication (9.43%) or other products taken concurrently by the patient (11.32%).
- The different kinds of DDIs can be classified according to the danger they represent and whether or not the benefits of the concurrent medication outweigh the risks.

Patients taking drugs which are not administered orally and continuously have, in general, a greater medical care, which makes these medicines a less immediate priority for inclusion in P.C.

Pharmaceutical Consultation Expansion: Short-term expansion

Taken Orally

- Because they are almost always taken by the patients themselves, there is a greater potential for incorrect therapeutic adherence.
- Injectable treatments are often administered by other health professionals, who also overlook the patients in some cases, reducing the need for added pharmaceutical care..

Taken Continuously

Medication taken continuously includes:

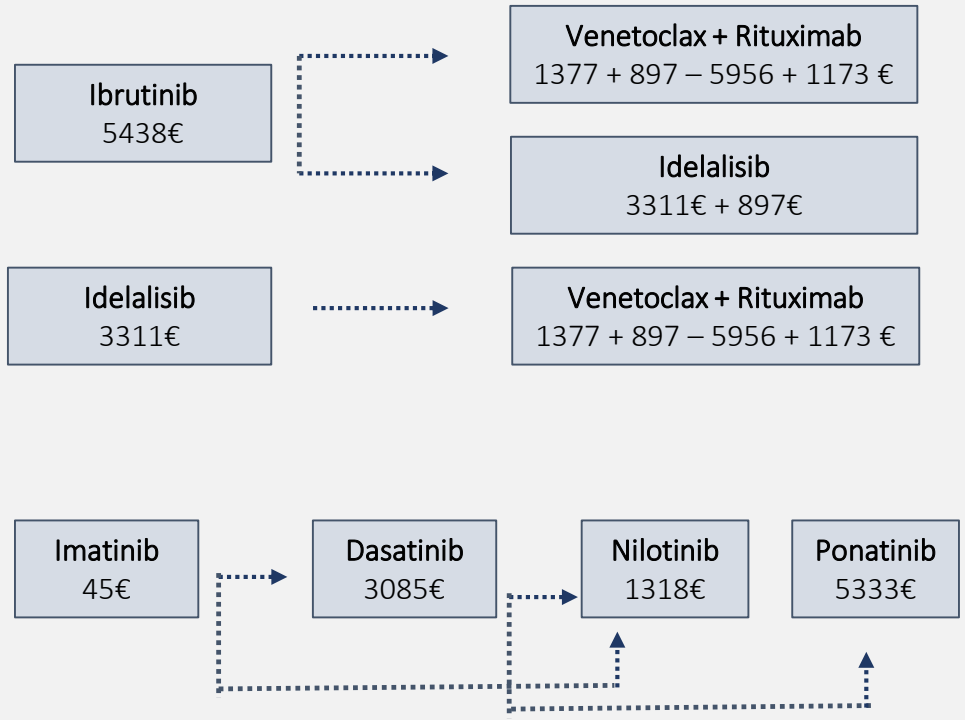
1) Drugs which are not only taken occasionally (e.g. antibiotics) → Due to being taken for a very short time period, it is not possible to observe evident effects of inadequate therapeutic adherence.

2) Drugs which are not taken cyclically (i.e. taken continuously for a certain period of time, followed by an interruption, after which the cycle is restarted) → In cyclical regimens, it is common for there to be dosage alterations between cycles, and the patients' progress must be analysed more frequently. As such, these patients will tend to receive closer medical support in comparison to those that take continuous medication, which makes them less urgent for inclusion in P.C.

Medication used in later treatment lines is, sometimes, substantially more expensive than the previous treatment line. Due to Imatinib's cost saving potential when patients take longer to advance to a 2nd line treatment and for being recommended by IPO's Haematology specialists, it has been selected as the highest priority drug to include in future P.C.

Pharmaceutical Consultation Expansion: Short-term expansion

Based on the previous criteria, we reach a final sample of **3** drugs. Assuming that, through additional pharmaceutical care, it is possible to increase the time outpatients spend before moving on to the next treatment line, it is fundamental to consider medicines which have **a more expensive option as the following line of treatment,** in order to maximize the institution's economic resources. The following costs were calculated for a 28 day period:



For not only following all the aforementioned criteria, but also for being recommended by interviewed Hematology doctors as the one which could bring higher benefits to patients from added pharmaceutical care, **Imatinib** has been selected as the most urgent medicine to add to the P.C. system.

Besides the data collected from the pharmacy distribution history for each patient, it is essential to understand how the medicine is applied to the different pathologies and the number of patients that rely on it annually.

Pharmaceutical Consultation Expansion: Short-term expansion

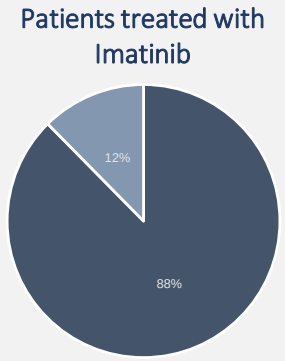
Cost Analysis (Savings) Model

The main data that needs to be considered in order to complete the cost study is:

- The T.R.R. percentages that were previously collected and inserted as inputs
- Definition of the most common lines of treatment for each pathology
- For each of the lines of treatment, identify the correspondent medicines and dosage, in order to estimate the monthly costs associated with them
- Obtain the average number of new patients that initiate treatment each year

Imatinib Case

When collecting this information for Imatinib, only values referring to 2017 were considered, since the information concerning 2018 was incomplete. In order to ensure that the analysis is trustworthy and resembles reality as much as possible, the data should be collected for as long a period as possible.



- **Chronic Lymphocytic Leukemia**
  - Line 1: Imatinib → 45€
  - Line 2 – most common: Dasatinib → 3085€
  - → Number of new patients 2017: **17**
- **Acute Myeloid Leukemia**
  - Line 1: Imatinib → 45€
  - Line 2: No records → N.A.
  - → Number of new patients 2017: **2**

The collection of this data allows verifying that the patients with LLA, besides representing a reduced number out of the sample of patients treated with this medicine, also represent only **11%** of **new patients** annually. Additionally, since they displayed a **TRR of 100%** on the 1st line throughout the entire analysed period, it is not possible to extract the historical cost of subsequent lines. This does not preclude that these patients could move on to the 2nd line in the future.

The time increment necessary due to the addition of Imatinib to the pharmaceutical care can be offset by the reduction verified by restricting the Ibrutinib consultation to the first 12 months

Pharmaceutical Consultation Expansion: Short-term expansion

Analysis Model

Study of changes of consultation time

The implementation of the pharmaceutical consultation alters the conditions in which the patient care will occur. Such will involve alterations on the time spent, both monthly and yearly, thus creating the need to evaluate whether the services have the necessary installed capacity to accommodate such demands.

Without Pharmaceutical Care				
Type of Consultation	Duration (minutes)	Number of Consultations (2017)	Total time (yearly)	Total time (monthly)
1st Consultation	10	17	170	14.2
Prescription Alteration	5	20	100	8.5
Simple Distribution	3	166.6	499.8	41.2
Total		**204**	**771.8**	**64.3**

*Assumption: The duration of the consultation does not change for new medications

With Pharmaceutical Care				
Type of Consultation	Duration (minutes)	Number of Consultations (2017)	Total time (yearly)	Total time (monthly)
1st Consultation	20	17	340	28.3
Subsequent Consultations	15	187	2805	233.8
Total		**204**	**3145**	**262.1**

<u>Yearly Variation</u>
In minutes
2373.2

In hours:
39.6

<u>Monthly Variation</u>
In minutes:
197.8

In hours:
3.3

- ✓ If the Imatinib patients are incorporated in the pharmaceutical care, the necessary time will increase **3.07 times**, which is translated into an annual increase of **39.6** hours, the equivalent to **3.3** hours per month.
- ✓ Due to the time saved in the Ibrutinib consultations by applying them only to patients within the first 12 months, it is possible to include the Imatinib patients **without exhausting the ambulatory service capacity,** thus presenting an opportunity cost of **zero.**

By identifying the activities with less relevance in the IPO pharmacy, it may be possible to sustain the expansion of the pharmaceutical consultations in the long run

Pharmaceutical Consultation Expansion: Short-term expansion

The opportunity cost analysis intends to investigate in which ways the time of the IPO pharmacists is allocated among the different activities performed in the pharmacy. Although , up to this moment, this analysis has not been required due to service optimization, which has allowed the accommodation of the consultations, this need will arise with the gradual increase of medicines, as the installed capacity will eventually run out.

1. Identification of Activities

- ✓ Construction of a flow chart that represents all the activities performed in the pharmacy, from the reception to the supply of medication.
- ✓ Considering that pharmaceutical consultations are an ambulatory activity, this service's main activities were also listed.

2. Prioritization of Activities

- ✓ Individual questionnaires to comprise a ranking that orders the activities from the most to the least essential within the service.
- ✓ Sum of the individual scores, in order to identify the least important activities with the greatest potential for replacement

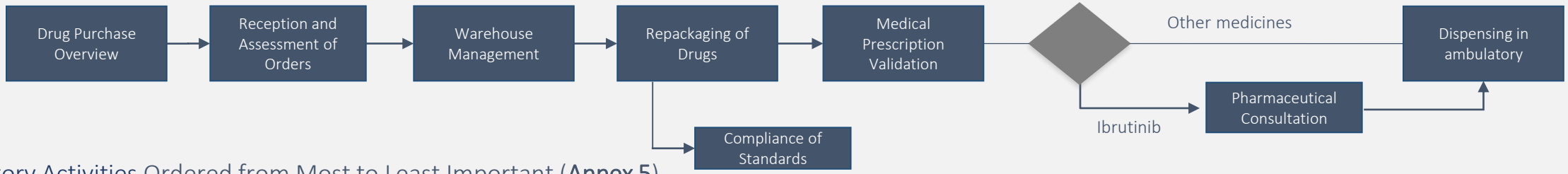
3. Determination of Opportunity Cost

- ✓ For the activities with the **lowest relevance**, it was established who could perform them aside from the pharmacist, and the **costs associated** with this procedure, aiming to **validate the financial sustainability** of this project in the long term as the number of patients increase.

The pharmacy activities include front office and back office tasks. Although the consultations are accommodated within the ambulatory activities, the expansion of this service will have an impact on the entire pharmaceutical paradigm

Pharmaceutical Consultation Expansion: Short-term expansion

Pharmacy Activities



Ambulatory Activities Ordered from Most to Least Important (Annex 5)

Ambulatory Care	Preparation of custom medication	Preparation of cytostatic drugs and other sterile substances
• <u>Distribution of Medicine</u>	• <u>Custom Medicine Preparation</u>	• <u>Preparation of parenteral nutrition, custom, and cytostatic drugs</u>
• Inventory management/Fill presence sheet	• Development of new custom medicines	• Drug stock management and medical devices
• Organize repackaging of outpatient drugs	• Custom Drugs and Raw Materials Stock Management (Back Office)	• Personnel training
• Production of information		• Monitorization of instruments and equipment
• Clinical trials		• Qualification and control of the working areas
		• Clinical trials

* The under-lined tasks represent front-office activities

On a first phase, a study coordinator should be hired as, within the set of options, it represents a lower cost while still being a sustainable option in the long run. Moreover, this ensures the continuity of the clinical trials, a high value activity for the hospital, due to the revenues generated.

Pharmaceutical Consultation Expansion: Short-term expansion

Through the prioritization of activities it is possible to understand that there is a range of activities within the pharmacy and the ambulatory services that can be entrusted to other health professionals. The related costs can be directly inputted to their salary :

	THERAPY DIAGNOSIS TECHNICIAN (1050 EUROS)	STUDY COORDINATOR (700 EUROS)	INTERN (0 EUROS)
Activities	**Pharmacy Activities** ✓ Reception and assessment of orders ✓ Order distribution ✓ Service consumption monitorization in each department **Ambulatory Activities – Preparation of cytostatic and other sterile drugs** ✓ Monitoring instruments and equipment ✓ Management of stocks and medical devices	**Pharmacy Activities** ✓ Performance of clinical trials both in the ambulatory care unit and in the preparation of cytostatic and sterile drugs	**Pharmacy Activities** ✓ Provision of information to doctors and nurses on behalf of pharmacists regarding the medicines **Ambulatory Activities – Patient Care** ✓ Production of information brochures, among others
Advantages	✓ **Wide range of activities**	✓ Financial burden considered **intermediate** ✓ **Specialized** in tasks that represent **high income*** for IPO	✓ **No direct financial burdens**
Disadvantages	✓ Relatively **high salary**	✓ **Limited** activity reach	✓ **Highly rotational and unstable** position (no contract) ✓ Process demands **continuous education** ✓ **Low** professional experience ✓ Only perform **sporadic** tasks in the context of the pharmacy

*The value of the **Clinical Trials**, in 2017, was approximately **37.778 euros** per month

In the case of a test scenario with Imatinib, P.C. will be profitable as long as they can contribute to helping 2 additional patients remain in the 1st line treatment. Performing similar analyses will be useful when considering which new drugs could lead to greater cost savings in P.C.

Pharmaceutical Consultation Expansion: Short-term expansion

OUTPUT:

Through this analysis it is possible to gain a perception of the impact that the variation in the number of patients that transition to the 2nd line has on the increase of the T.R.R. and how that may generate savings.

These metrics may be useful by providing savings expectations for when the project is implemented, and may also help in the decision-making process, for when new medicines are considered to be implemented in the program. A detailed explanation of the steps in the Excel which lead to the creation of the **Estimation Model** is included in **Annex 6.**

Imatinib Case no Investment

Absolute patient increase in 1st line	Variation in 1st line T.R.R	Value net of Investment = NPV
1	*+0,30 %*	5.588,65 €
2	*+0,60 %*	11.299,69€
3	*+0,89 %*	17.135,88€
4	*+1,19 %*	23.100,09€
5	*+1,51 %*	26.669,61€

Imatinib Case assuming a Study Coordinator is hired → **Investment:** *Monthly: 700€*
*Annual:9.800€**

Absolute patient increase in 1st line	Value net of Investment	Net Present Value	Cost - Effectiveness
1	5.588,65 €	-4.211,65 €	1,75
2	11.299,68€	1.49,68 €	0,87
3	17.135,88€	7.355,88 €	0,57
4	23.100,09€	13.300,06 €	0,42
5	26.669,61€	19.869,61 €	0,33

Under this scenario, P.C will be profitable if two extra individuals remain in Line 1

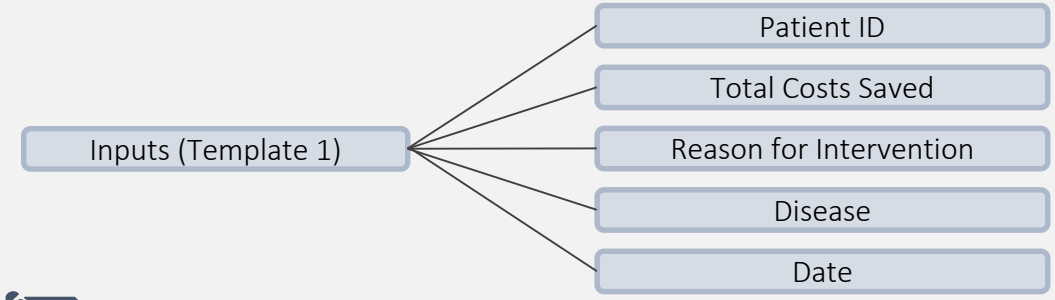
*Assuming 14 months due Holiday and Christmas subsidies

Through the usage of the provided excel files, a methodical gathering and organization of relevant data can be performed.

Pharmaceutical Consultation Expansion: Short-term expansion

Data Collecting and Processing

After the pathologies associated with the studied medicine are identified, it is possible to start retrieving the data necessary to perform the analysis



Disease		
Number of Patient		
Date	Change of Dosage/Interaction	Variation
01/01/2000	XXX	0/1

Example of input label

T.R.R construction and Markov Chain Systemization

Number of 1st line patients at **END** of period

Number 1st line patients at **BEGINNING** of period

→ T.R.R of the period → BASE MARKOV CHAIN

→ **SYSTEMIZATION:** Calculation of 1st twelve months average → Systemized T.R.R → NORMALIZED MARKOV CHAIN

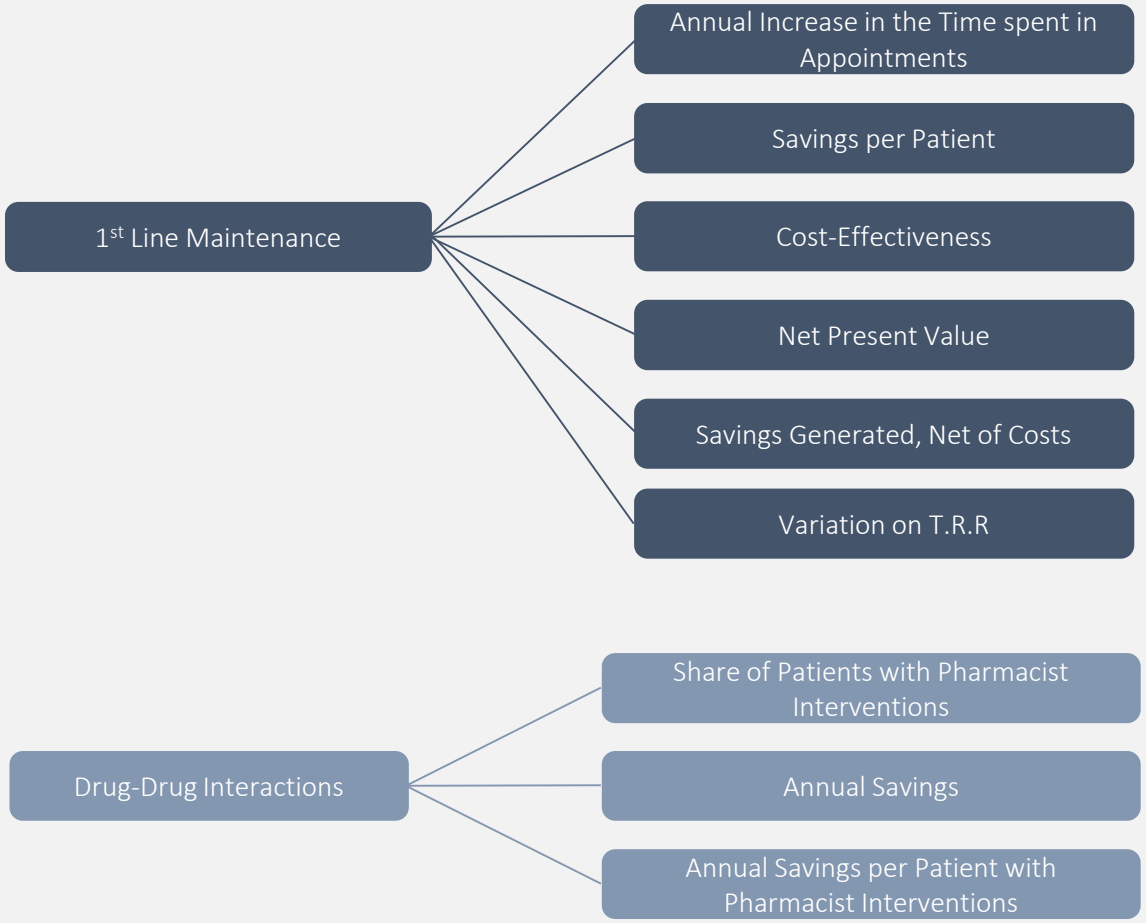
	Complete Processes				
	Line 1			Subsequent Lines	
	Line 1 END OF PERIOD	Line 1 START	T.R.R 1 %	Line 2 END OF PERIOD	T.R.R. 2 %
Date 1	32	32	100,0%	0	0,0%
Date 2	32	32	100,0%	0	0,0%
Date 3	32	32	100,0%	0	0,0%
Date 4	31	32	96,9%	1	3,1%
Date 5	29	32	90,6%	3	9,4%
Date 6	32	32	100,0%	0	0,0%
Date 7	27	30	90,0%	3	10,0%
Date 8	25	27	92,6%	2	7,4%
Date 9	25	26	96,2%	1	3,8%
Date 10	23	24	95,8%	1	4,2%
Date 11	24	24	100,0%	0	0,0%
Date 12	24	24	100,0%	0	0,0%

Detailed manual is included in **Annex 1**

The provided excel file allows calculating financial indexes pertaining to the cost benefits of having patients stay longer within their 1st line treatment and the detection of DDIs which imply dosage adjustments.

Pharmaceutical Consultation Expansion: Short-term expansion

Cost Analysis (Savings) Model

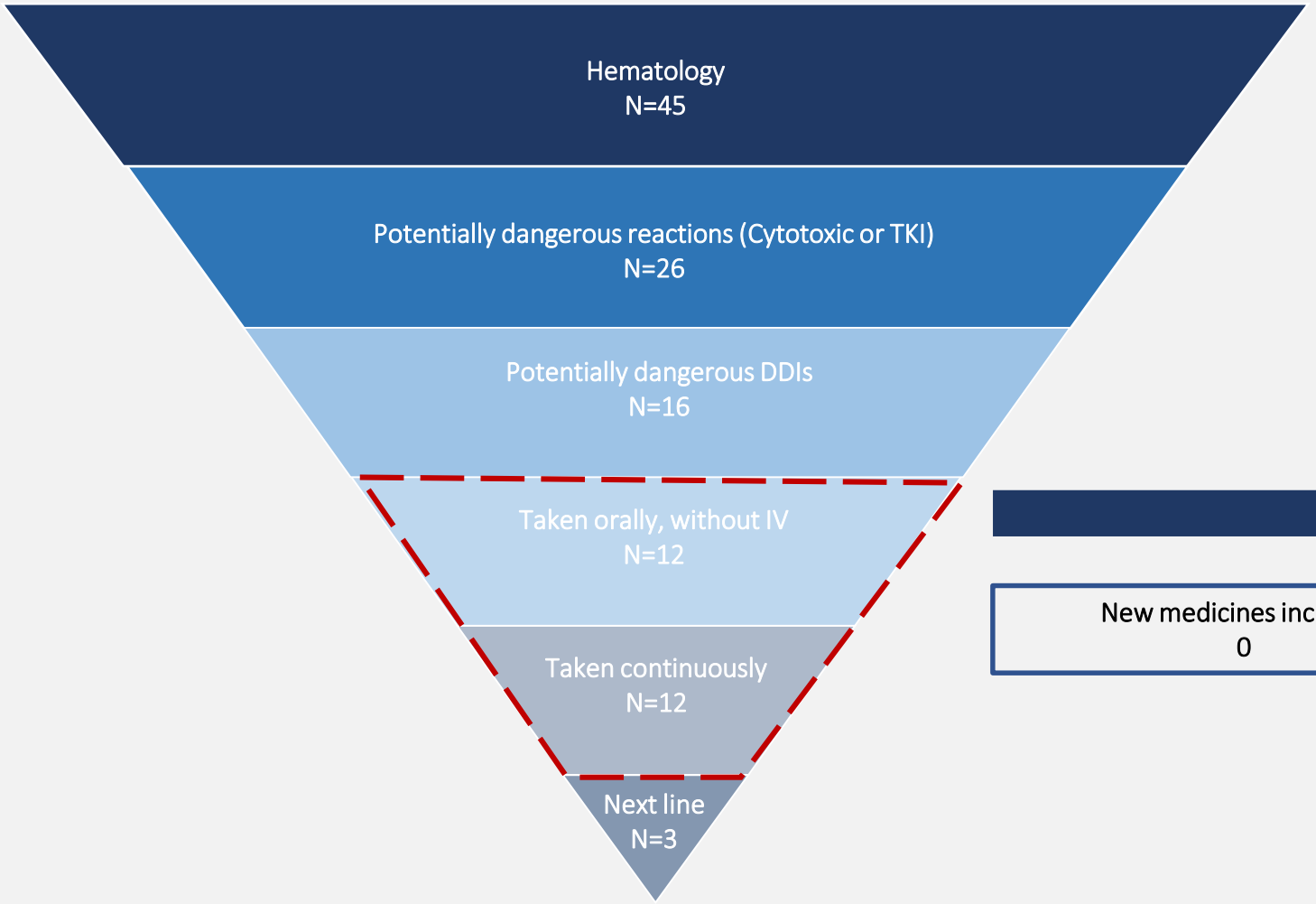


	xxx	xxx	xxx	xxx
Annual Saving Net of Inv.	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
N.P.V	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Cost-effectiveness	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
# of Patients	19	17	0	0
Saving per Patient	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Annual Hour increase	44,21	39,55	-	-
Monthly Hour Increase	3,68	3,30	-	-

Average Number of Patients	
Annual Numer of New patients	
Patients with Intervention	
Number of Interventions	
% of Patients with intervention	
Average Value of Intervention	
Annual Saving (new patients)	
Monthly Saving (new patients)	

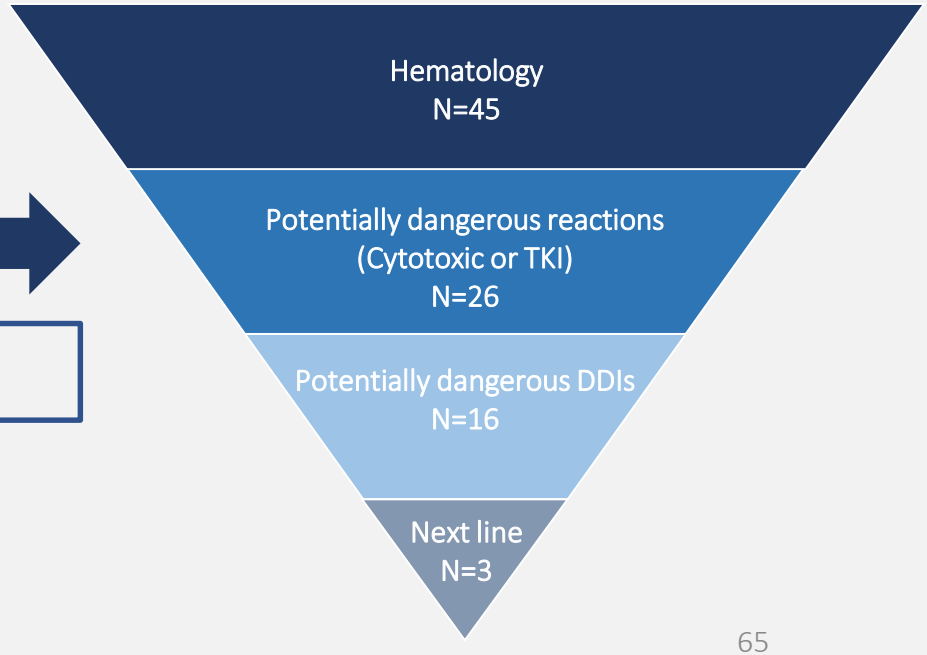
In the first expansion phase, the “taken orally” and “taken continuously” decision criteria will be dropped. Of the 4 additional drugs considered after this change, none of them possesses a more expensive next line treatment.

Pharmaceutical Consultation Expansion: Long-term expansion



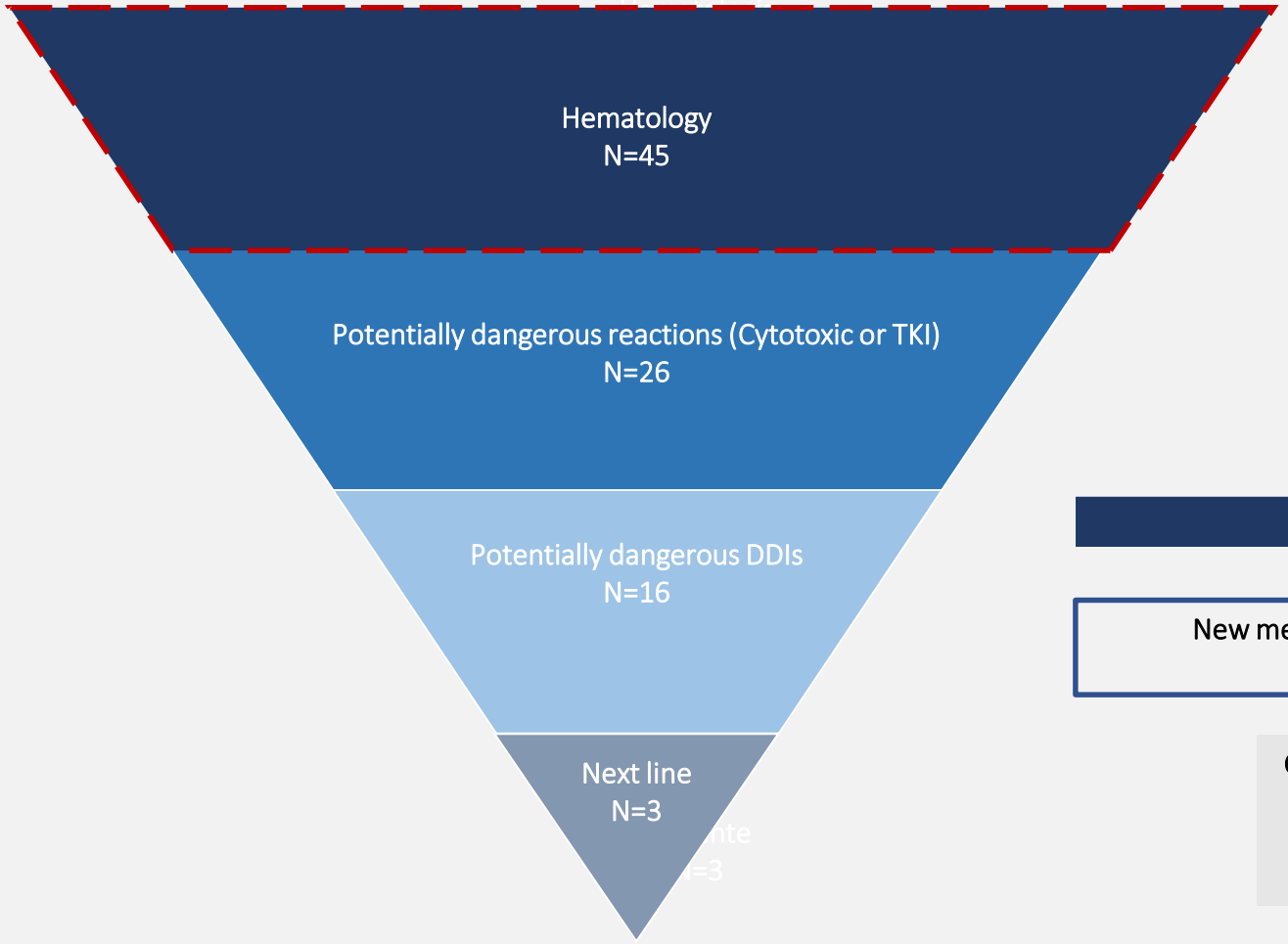
New medicines included:
0

After adding Imatinib and Idelalisib to the P.C., it was decided in conjunction with IPO’s pharmacists that the less essential criteria, the first to be dropped, would be “Taken Orally” and “Taken Continuously”.



In the 2nd expansion phase, the remaining criteria will now also be applied to non-hematological drugs, which will lead to including 4 new medicines within the scope of P.C.

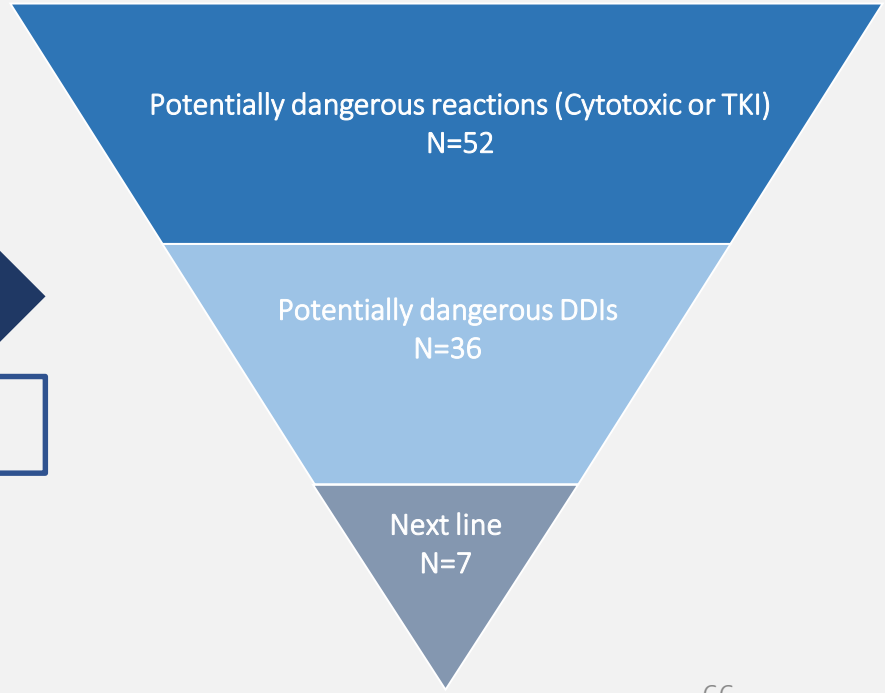
Pharmaceutical Consultation Expansion: Long-term expansion



New medicines included:
4

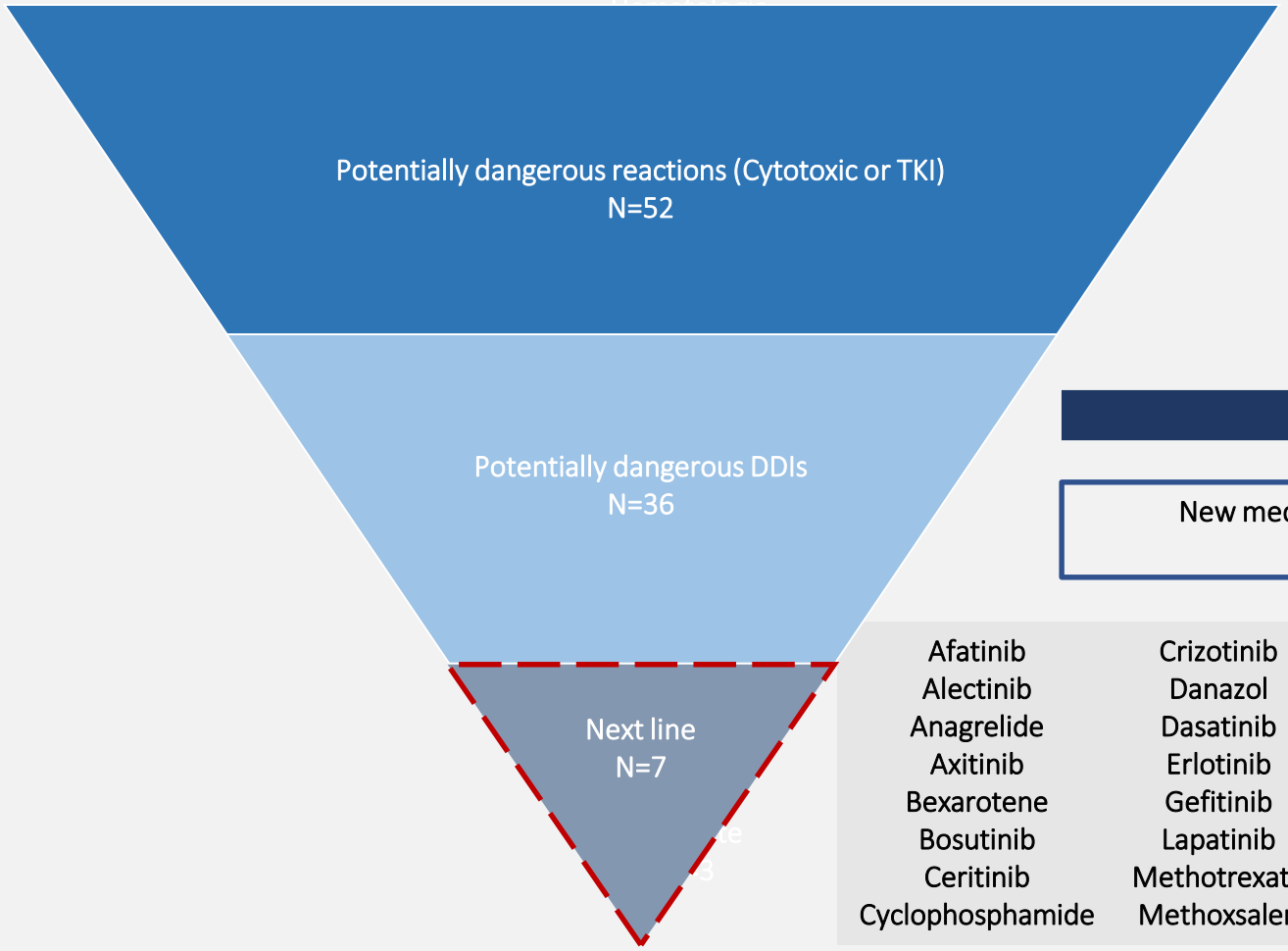
Capecitabine
Cobimetinib
Sunitinib
VePCafenib

In the 2nd phase, the main goal is to add non-hematological medication which simultaneously represent a high potential risk to patients and have a more expensive next line treatment.



In the 3rd phase, only the most crucial factors impacted by pharmaceutical monitoring will be maintained. This phase will imply gradually adding 29 new drugs to the P.C.

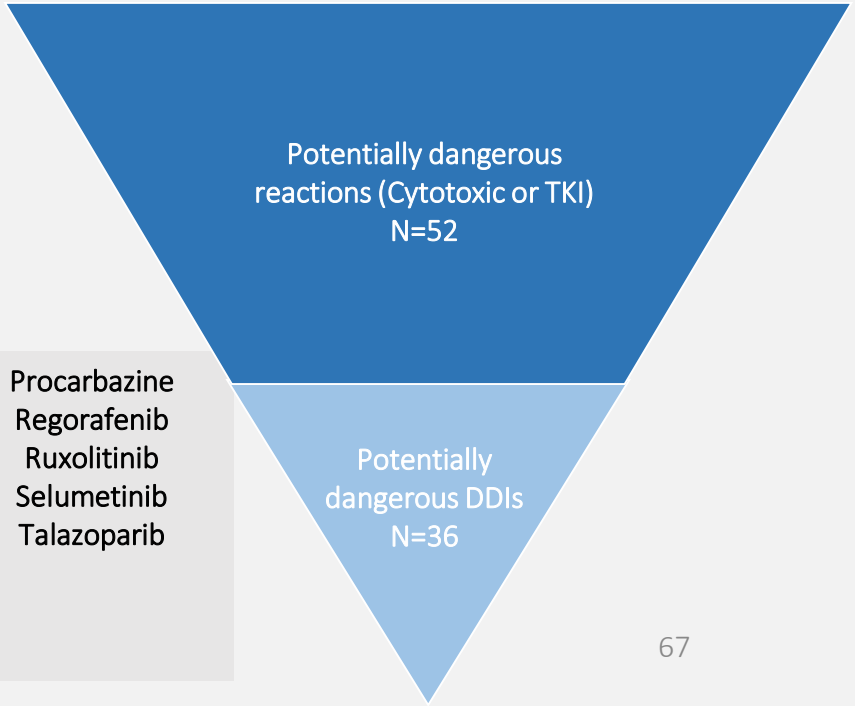
Pharmaceutical Consultation Expansion: Long-term expansion



New medicines included:
29

Afatinib	Crizotinib	Midostaurin	Procarbazine
Alectinib	Danazol	Nilotinib	Regorafenib
Anagrelide	Dasatinib	Olaparib	Ruxolitinib
Axitinib	Erlotinib	Osimertinib	Selumetinib
Bexarotene	Gefitinib	Palbociclib	Talazoparib
Bosutinib	Lapatinib	Pazopanib	
Ceritinib	Methotrexate	Pomalidomide	
Cyclophosphamide	Methoxsalen	Ponatinib	

In the 3rd phase, all medication with potential adverse reactions and interactions with other drugs will be included, as these are the core factors upon which pharmaceutical care can cause the greatest impact. Given the high number of additional drugs this phase will bring, it will be necessary to consider a new prioritization, either according to their medical specialty or their relative risk to the patient.



AGENDA

AGENDA

7 Change Management - Internal and External Stakeholders

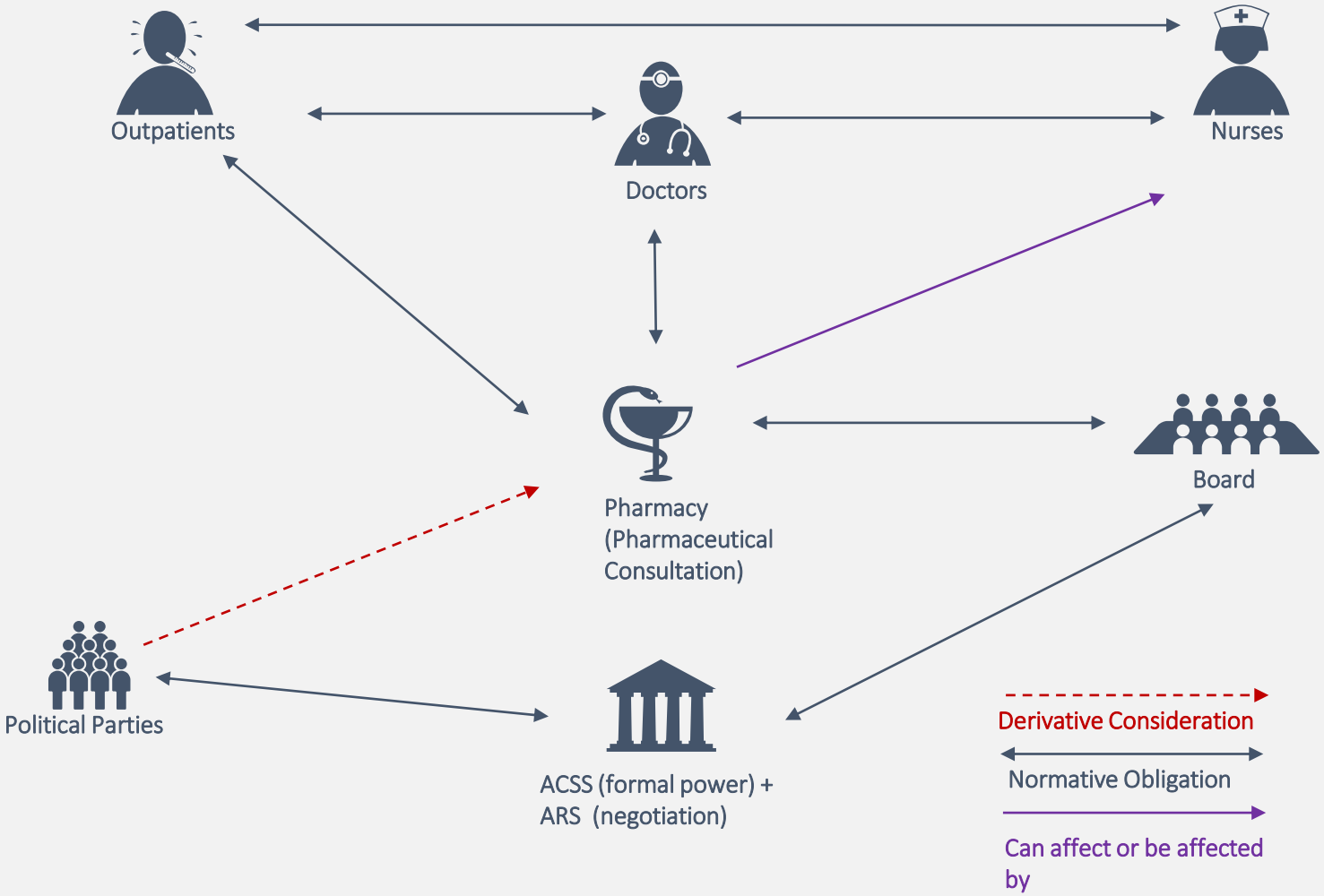
i. Relationship
ii. Stakeholder Mapping
iii. Stakeholder Strategies

Given IPO's dynamic ecosystem, it is essential to consider how the different parties potentially related to the P.C. are interconnected.

Change Management - Internal and External Stakeholders: Relationships

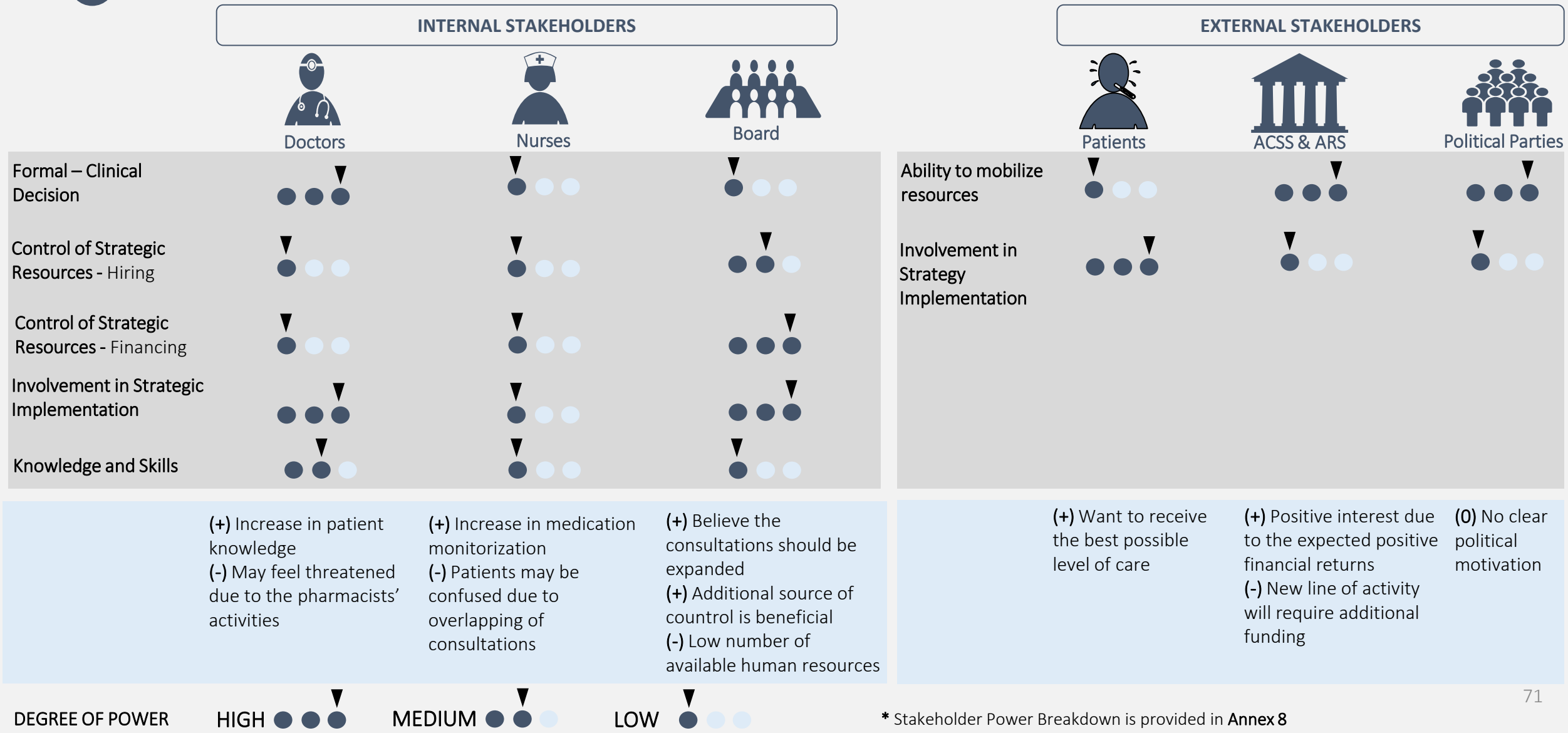
- The expansion of **Pharmaceutical Consultations** requires taking into account the **several parties** within the dynamic and **complex ecosystem** of IPO.
- By understanding these parties' **expectations, level of influence,** and **interdependence**, it is possible to identify **key stakeholders** concerning the **expansion of pharmaceutical consultations. A listing and rationale** behind the parties chosen in included in **Annex 7**.
- By knowing each group's **positions** within the greater **relationship scheme** we can define **strategies** to smoothen **implementation and expansion**
- **IPO stakeholders** can be split into two categories:
  - External Stakeholders
    - **ACSS + ARS** (Government Body)
    - **Political Parties**
    - **Outpatients**
  - Internal Stakeholders
    - **Board**
    - **Nurses**
    - **Doctors**

Relationship Map



When evaluating the degree of power of each stakeholder, both formal and informal power sources were considered. Positive and negative interest motivators were also taken into account.

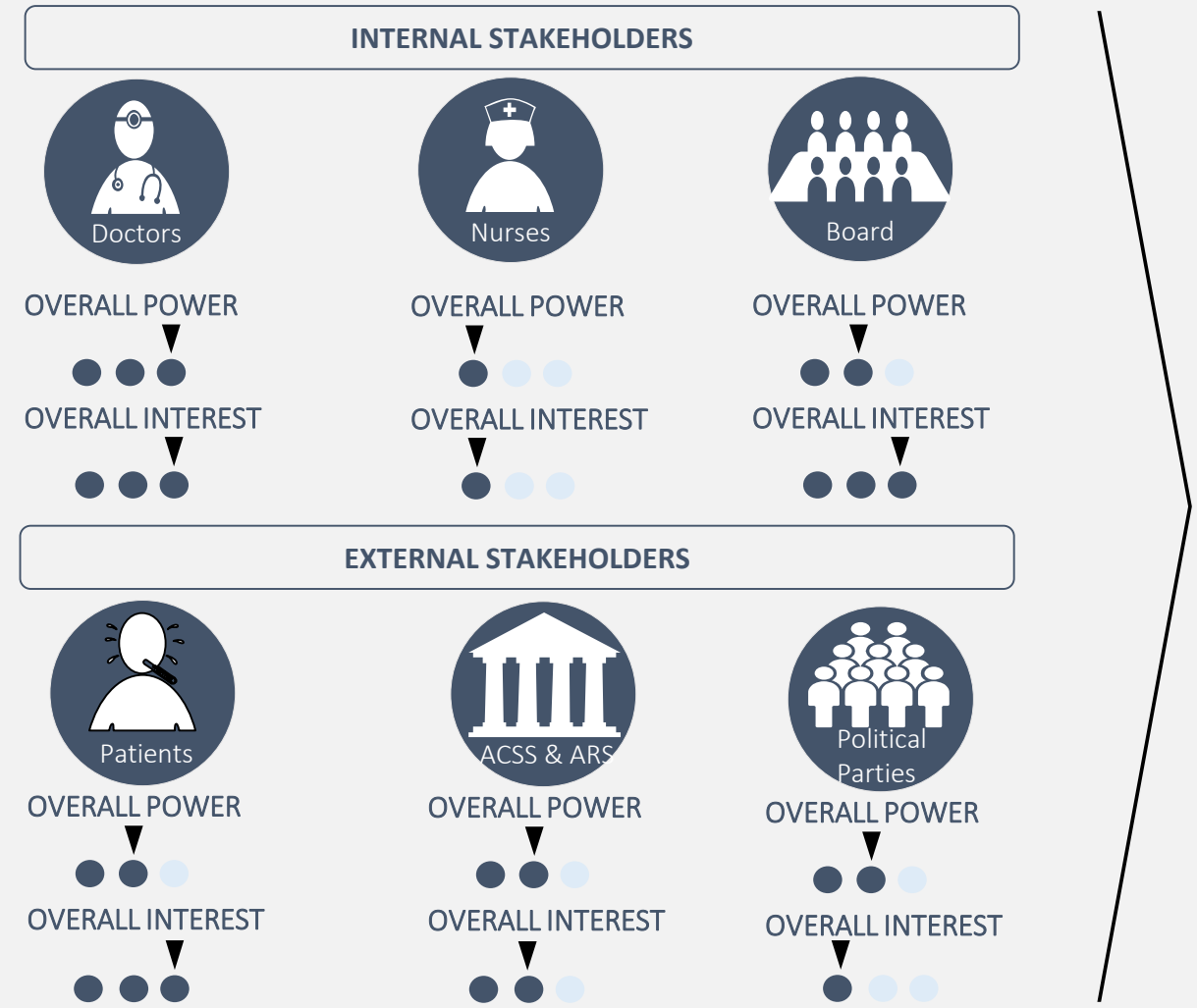
Change Management - Internal and External Stakeholders: Stakeholder Mapping

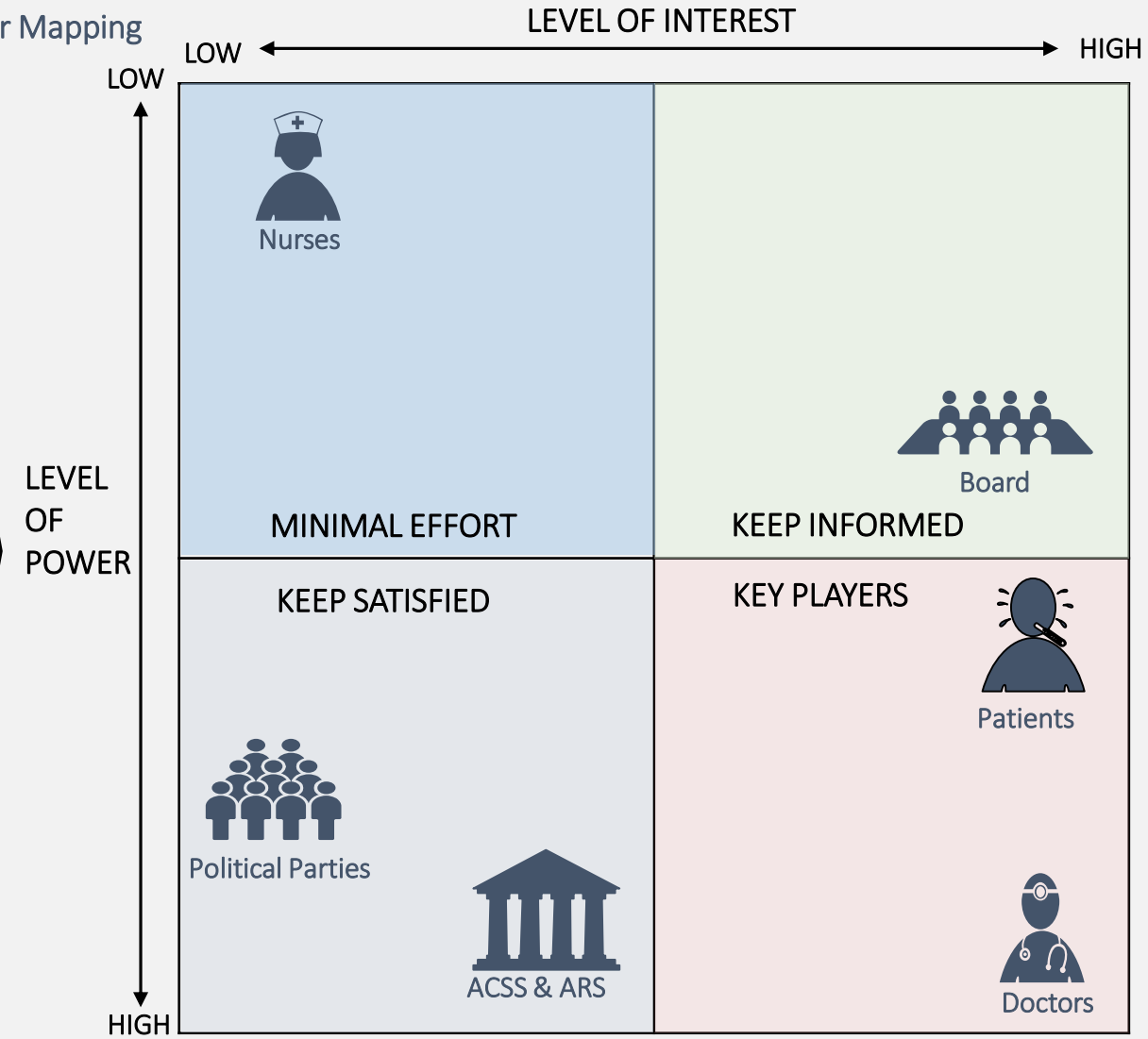


* Stakeholder Power Breakdown is provided in **Annex 8**

Stakeholder mapping suggests that patients and doctors are the two most important key groups, and their outlook towards P.C. will greatly influence the future success of this initiative.

Change Management - Internal and External Stakeholders: Stakeholder Mapping





* Stakeholder Interest Breakdown is provided in **Annex 9**

Change Management - Internal and External Stakeholders: Stakeholder Strategies

Taking into consideration the **interests** and **powers** of the several stakeholders, the following **strategies** were identified:

- **Minimal effort** regarding **implementation**, but try to establish lines of communication in order to i**mprove patient outcomes** through **multidisciplinary cooperation**.
- Establish **clear boundaries** between **pharmaceutical** and **nursing** consultations.

- Keep them **updated on new developments** related to verified **benefits** of the pharmaceutical consultations in order to **drive engagement** and **keep interest high.**

- Although there is little direct contact between them and the pharmacy, attempt to **raise interest level** through the **social impact** of the consultations.

- Attempt to reach a **higher level of interest** by sharing the observed **clinical** and **financial benefits** of the **pharmaceutical consultations.**

- Explain the **main caracteristics** and **clinical benefits** of pharmaceutical consultations in a clear manner to keep their **engagement high**.

- Define a **message** according to the **personal policies and priorities** of **each doctor**.
- Establish **clear positions** and **goals** for the **pharmaceutical consultation**.
- Share the **main results** achieved through pharmaceutical consultations.

Stakeholder Classification Minimal Effort | Keep Satisfied | Keep Informed | Key Player

AGENDA

Due to challenges faced in data collection, final outputs do not include cost saving estimates due to 1st line maintenance variations. However, the required tools to accomplish this analysis and the necessary know-how will be transferred to IPO's professionals.

Limitations, Implementation, and Mitigation

- Although the Ibrutinib P.C. began with both a control group and a research group, **after the first 4 months** the patients within the control group were **gradually included in the research group**, due to **ethical concerns** on excluding some patients from the consultation's **clinical benefits.**
- Due to the **lack of a stable control group** for the Ibrutinib P.C. throughout its 2 years of implementation, it was **not possible to verify** to what extent patients with consultations **remained longer within the 1st line treatment**.
- In an attempt to overcome this lack of data we questioned **Hematology doctors** on their **estimates** as to the possible **impact** these consultations had upon the **patients' 1st line maintenance**, however, the overall outlook was that the **P.C. had not been operating long enough** to allow them to form a conclusion. As such, they did not feel confident enough to form assumptions on this matter.
- On a later attempt to obtain a group for comparison, we contacted **IPO Porto** and requested **anonymous Ibrutinib patient data** which would let us **build a scenario without P.C.** and analyse the extent of the clinical benefits of these consultations. Unfortunately, due to **ethical and confidentiality concerns**, this request would have to undergo the approval of the institution's **Ethics Committee**, which would be a **lengthy process** beyond the scope of this project.
- Even though it was possible to **estimate cost savings based on hypothetical scenarios**, several Health experts **discouraged that approach** as there would be **no guarantee for the usefulness of the obtained results**.
- Taking all of the above factors into account, we focused on creating a **decision-making tool**, in the form of several **excel documents** accompanied by an **instruction manual**, with which IPO's pharmacists can be empowered to easily **input data of future control and research groups** of different medications and automatically **obtain predicted cost savings**.

The implementation of Pharmaceutical Consultations requires a short and long-term plan, which starts by releasing Pharmaceutical Consultation long-term Ibrutinib patients

Limitations, Implementation, and Mitigation

	# months	1 month	3 months	6 months	9 months	12 months
Release long-term patients						
Analyse the patients that will remain in the Pharmaceutical Consultation	1					
Notify and transfer responsibilities to long-term patients	3					
Announce the changes to the clinical staff	1					
Imatinib Pilot						
Align expectations with the clinical staff	3					
Produce a detailed medication brochure to educate the patient	3					
Create a survey to determine the level of education of the patient before starting the drug	3					
Analysis of the expansion of PC						
Expansion of the several drug typologies	3					
Expansion of the pharmaceutical consultation to other types of drugs	Cont.					

By limiting the Pharmaceutical Consultation to the first 12 months of treatment, the pharmacy gains added installed capacity which is fundamental for the expansion to other drugs. The risks to this measure can be minimized by maintaining a clear line of communication between pharmacists and patients

Recommendation #1: Release long-term ibrutinib patients

RATIONALE

- Most pharmaceutical interventions happened during the first year of drug administration

PROS

- Gains in terms of installed capacity in the pharmacy
- Opportunity to expand Pharmaceutical Consultation to other drugs
- It becomes easier to predict the required time when expanding Pharmaceutical Consultation to other drugs

RISKS	MITIGATION OF RISKS
Patients may start taking new concomitant drugs after the 12th month	Explain to the patient the conditions under which they should request a new Pharmaceutical Consultation
New doubts may arise after the 1st year	Notify the patient that he should contact the pharmacy in the event of new doubts
Ethical problems could arise since Pharmaceutical Consultations will not include all patients	Further analysis should be performed with the goal of clarifying whether there are clinical benefits to the patient beyond the first year

The creation of a pilot for Imatinib will further expand the know-how required for other drug expansions. Risk-mitigation will provide a clear path for new additions

Recommendation #2: Imatinib Pilot

RATIONALE

- Evidence points out that Pharmaceutical Consultations have economical and clinical benefits
- Speciality doctors welcome the application of Pharmaceutical Consultations to this drug

PROS

- Drug with a high level of toxicity to the patient
- Drug with a high number of DDIs
- Potential economic gains

RISKS	MITIGATION OF RISKS
The patient might not understand the need for the Pharmaceutical Consultation	Clearly determine the expected benefits with the patient, answering all doubts
Information sharing between pharmacy and clinical staff	Endorse a transparent line of communication between stakeholders
Insufficient installed capacity	Delegate secondary tasks to other agents
Quality and decentralization of the records	Establish quality metrics for records taken

The greatest challenge concerning the expansion of drugs is related to instaled capacity required to attend patients. When limitations arise, adding an additional pharmacist as back office support should be considered.

Recomendation #3: Future expansion

RATIONALE

- After consolidating drugs with higher value, it is important to include others that present a high level of risk

PROS

- After including new drugs, the process will be simplified
- If additional drugs present clear clinical and/or economical opportunities, then there is no reason to not explore them

RISK	MITIGATION OF RISKS
The implementation of phase 3 provides many constraints to the installed capacity	Prioritize drugs with a higher level of level of danger to the patient
Difficult to adapt the required installed capacity even after hiring a therapy diagnosis technician	Consider reorganizing the activities of the ambulatory care with the goal of having an additional pharmacist to support back office tasks
Danger of the process being blocked due to stakeholder action	Identify the stakeholder's motivations and establish a strategy in order to respond appropriately

AGENDA

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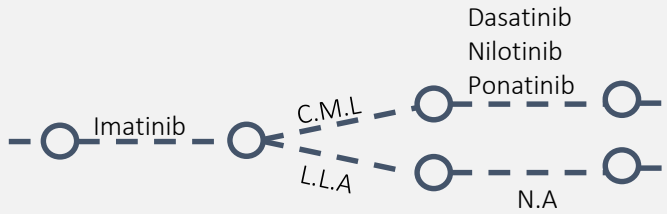
Thank You

Q & A

As Imatinib has been detected as the most suitable candidate to be incorporated in the pilot project of the pharmaceutical consultations, the mathematical estimation model previously described for Ibrutinib was applied to this medicine in order to evaluate its financial and economic viability

1 . Identification and Analysis of different pathologies treated with the medicine

- ✓ The aim is to perform an analysis that represents in the most reliable way the reality of the medicines supplied in the ambulatory service. For each medicine, the different pathologies and possible therapeutic lines must be identified. In this way, it is possible to estimate the savings associated with monitoring the patients in the respective lines.



- ✓ In the concrete case of Imatinib, it was verified that it was used for patients suffering from **Chronic Myeloid Leukemia (CML)** and **Acute Myeloid Leukemia (AML)**

- ✓ The proportion of patients with **CML represent**, for the period analysed, over **87% of the sample**, whereas for **AML patients** there **is no record of progressing to the second line** of treatment throughout the 18 month period considered. Hence, the study will merely focus on patients with CML on the first phase of the project.

2 . Collection of Data

The first step consists in creating a normalized historical record for all patients. Thus, it is necessary to download the data relative to the pharmacy distribution history for each of them, and introduce it in the Excel file Template 01. The following elements must be specifically collected:

- **Patient ID Number** – in case there is a need to verify any anomalies, the patient number facilitates the cross-checking between the different hospital platforms that contain clinical data
- **Distribution date** – allows checking the frequency with which the patient withdrew the medication
- **Medicine as dosage** – allows verifying which are the most frequent subsequent lines of treatment and when changes in dosage occur
- **Variation** – in the periods in which the patient stays in the same line of treatment, a number **0** is inputted, while a number **1** is registered when the medication used is altered

LMC			LMC		
1232736			1232865		
Data	ão dosagem/Inte	Variação	Data	ão dosagem/Inte	Variação
19/04/2018	3, MESILATO 4(	0	29/03/2018	3, MESILATO 4(	0
03/05/2018	3, MESILATO 4(	0	19/04/2018	3, MESILATO 4(	0
17/05/2018	3, MESILATO 4(	0	25/04/2018	3, MESILATO 4(	0
30/05/2018	3, MESILATO 4(	0	10/05/2018	3, MESILATO 4(	0
04/07/2018	3, MESILATO 4(	0	15/05/2018	OTINIB 200MG	1
02/08/2018	3, MESILATO 4(	0	05/06/2018	OTINIB 200MG	0
			03/07/2018	OTINIB 200MG	0
			24/07/2018	OTINIB 200MG	0

3 . TRR Calculation

Once the data from all patients is collected and consolidated, it is possible to infer, for each period, how many patients were in each line of treatment in the beginning and in the end. This is meant to calculate, in the case of the first line, how many of the patients that started the period on that line remained on the 1st line and how many transitioned to the 2nd.
Afterwards the formula that retrieves the TRR can be applied.

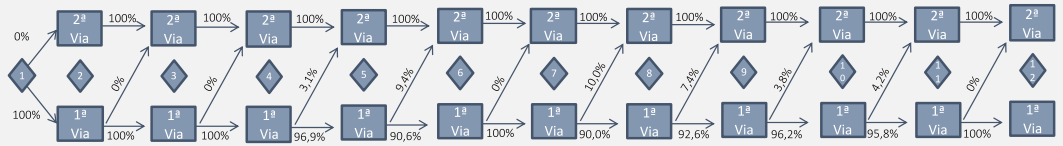
These values should then be copied and pasted on the Input sheet of Excel Template 02, and will be the basis for the cost computation that will allow for the savings study.

	Processos completos				
	ESTUDO PRIMEIRA VIA			ESTUDO VIAS ALTERNATIVAS	
	Mantiveram 1ª Via	Total	T.R.R 1ª %	Alteraram2ª via	T.R.R. 2ª %
Data 1	32	32	100,0%	0	0,0%
Data 2	32	32	100,0%	0	0,0%
Data 3	32	32	100,0%	0	0,0%
Data 4	31	32	96,9%	1	3,1%
Data 5	29	32	90,6%	3	9,4%
Data 6	32	32	100,0%	0	0,0%
Data 7	27	30	90,0%	3	10,0%
Data 8	25	27	92,6%	2	7,4%
Data 9	25	26	96,2%	1	3,8%
Data 10	23	24	95,8%	1	4,2%
Data 11	24	24	100,0%	0	0,0%
Data 12	24	24	100,0%	0	0,0%

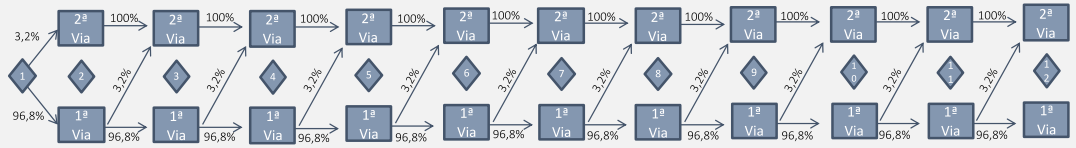
3 . 1 . Construction and Systematization of Markov Chains

After obtaining the TRR it is possible to assemble the Markov Chains corresponding to the different scenarios previously determined. These, however, constitute an initial scenario that assumes the exact probabilities at each date. With the purpose of systematizing the analysis and simplifying the predictions for the following periods, normalized chains were produced. The later consider the average of the first 12 months' TRRs instead of the real value for each period. The application of this methodology represents, *ceteris paribus,* a variation lower than 1% in the annual costs.

Initial Chain



Normalized Chain



Annex XXX – Excel Instruction Manual

Prediction Model

Since the analysis model can only be executed after the pharmaceutical care is implemented over a long enough period, in order for the data retrieved to be representative, a prediction model was created. In this model, it is possible to verify, for different scenarios, the variations of the T.R.R. and, consequently, the potential saved amount if the effective number of patients transitioning to the subsequent line decreases, within a possibility spectrum.

In order to perform a conservative analysis, these alterations should be done in the earlier periods, as long as possible, given that the overall number of patients is higher, hence the variations on the T.R.R will be slimmer and the same will happen to the cost reduction.

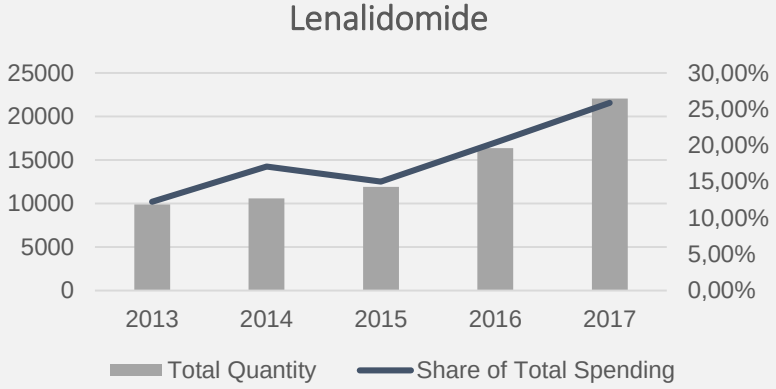
INPUTS:

The performance of this analysis only requires the adaptation in "*DEPOIS*" to the intended number of patients for the scenario the pharmacists want to consider.

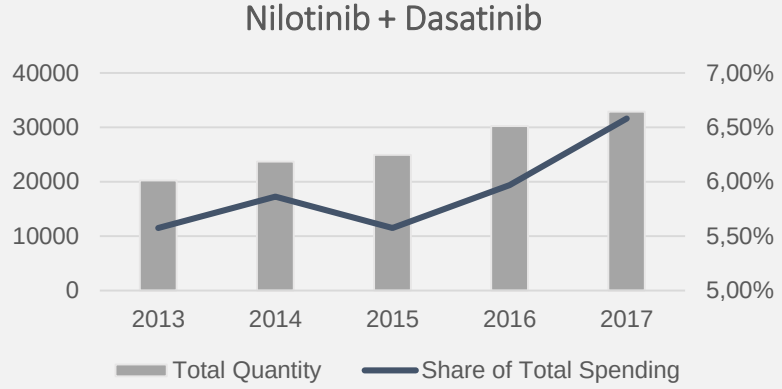
The value must be within the number of patients that were in the 1st line in the initial case and the total number pf patients. For the later, when the values coincide, the cells turn red and cannot be further increased.

To facilitate the enumeration, there are boxes below them that count the total number of changes performed.

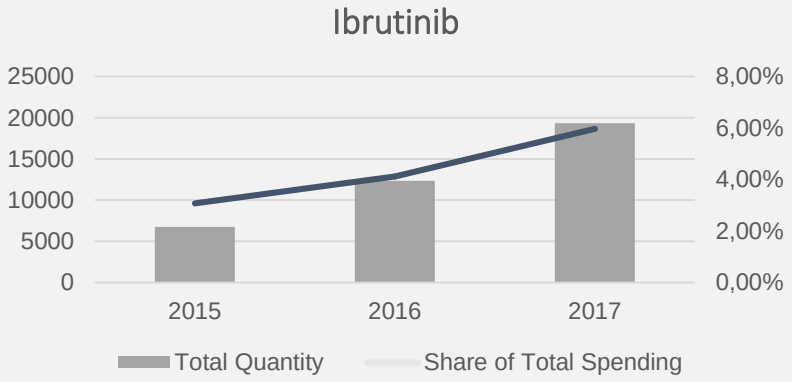
Data	Sem consulta		Manter mais 1 pessoa		Manter mais 2 pessoas		Manter mais 3 pessoas		Manter mais 4 pessoas		Manter mais 5 pessoas	
	Pessoas 1ª Via	Pessoas Total	Antes	Depois	Antes	Depois	Antes	Depois	Antes	Depois	Antes	Depois
1	32	32	32	32	32	32	32	32	32	32	32	32
2	32	32	32	32	32	32	32	32	32	32	32	32
3	32	32	32	32	32	32	32	32	32	32	32	32
4	31	32	31	32	31	32	31	32	31	32	31	32
5	29	32	29	29	29	30	29	31	29	32	29	32
6	32	32	32	32	32	32	32	32	32	32	32	32
7	27	30	27	27	27	27	27	27	27	27	27	28
8	25	27	25	25	25	25	25	25	25	25	25	25
9	25	26	25	25	25	25	25	25	25	25	25	25
10	23	24	23	23	23	23	23	23	23	23	23	23
11	24	24	24	24	24	24	24	24	24	24	24	24
12	24	24	24	24	24	24	24	24	24	24	24	24
			Variação		Variação		Variação		Variação		Variação	
			1		2		3		4		5	



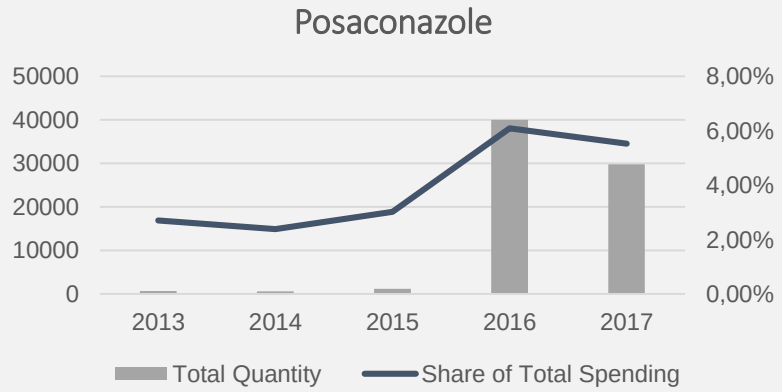
Evolution of Lenalidomide in the last 5 years



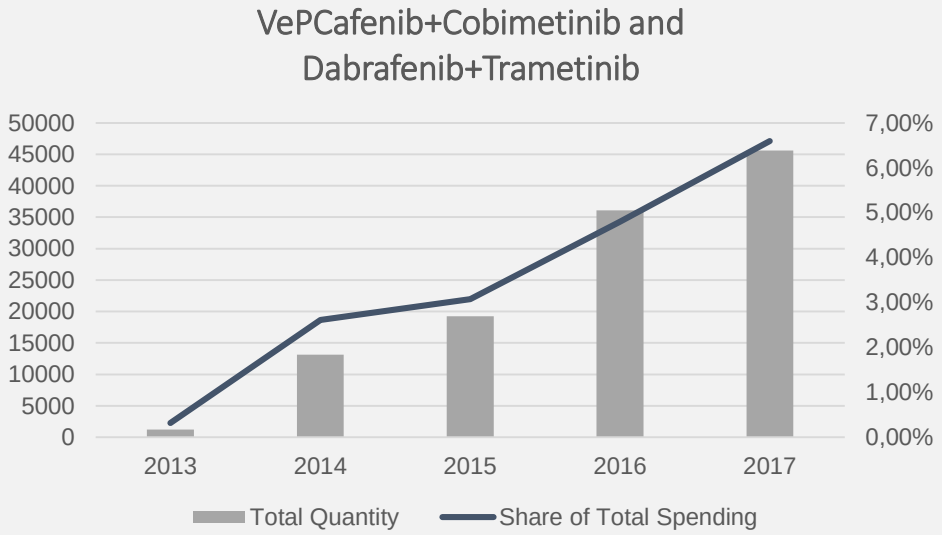
Evolution of Dasatinib + Nilotinib in the last 5 years



Evolution of Ibrutinib in the last 3 years



Evolution of Posaconazole in the last 5 years



Evolution of VePCafenib+Cobimetinib and Dabrafenib+Trametinib in the last 5 years

Annex 3 – List of Excluded Patients (Patient ID Partially Censored) and Motives

Excluded patients	Motive for Exclusion
593xxx	Only included in P.C. after beginning treatment
804xxx	Only included in P.C. after beginning treatment
847xxx	Only included in P.C. after beginning treatment
1002xxx	Only included in P.C. after beginning treatment
1037xxx	Only included in P.C. after beginning treatment
1065xxx	Could not come to the pharmacy in person
1077xxx	Insufficient records
1082xxx	Insufficient records
1098xxx	Insufficient records
1106xxx	Only included in P.C. after beginning treatment
1136xxx	Insufficient records
1136xxx	Insufficient records
1141xxx	Insufficient records
1149xxx	Only included in P.C. after beginning treatment
1154xxx	Insufficient records
1155xxx	Insufficient records
1163xxx	Insufficient records
1183xxx	Insufficient records
1194xxx	Insufficient records
1200xxx	Insufficient records
1201xxx	Insufficient records
1205xxx	Insufficient records
1208xxx	Insufficient records
1212xxx	Insufficient records
1218xxx	Insufficient records

A demographic study was done with the goal of having a more compreehensive understanding of the sample used towards performing the analysis.

Mantle cell lymphoma

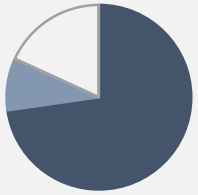
Sample Size: 13 outpatients

GENDER

Female **25%**

Male **75%**

CIVIL STATUS

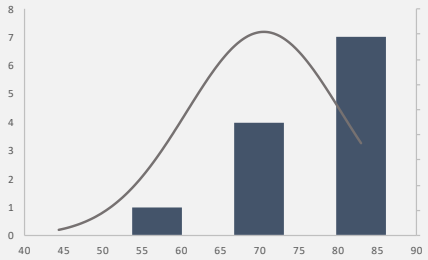


- Married **72,73%**
- Single **9,09%**
- Undetermined**18,18%**

AGE

8,33% <60
33,33% [60 – 70[
58,33% >70

$\bar{x} = 70{,}5$; s=9,82



Chronic Lymphocytic Leukaemia

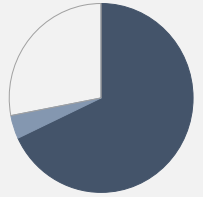
Sample Size: 24 outpatients

GENDER

Female **60%**

Male **40%**

CIVIL STATUS

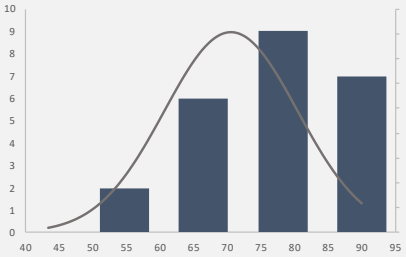


- Married **68,00 %**
- Single **4,00%**
- Undetermined**28,00%**

AGE

16,67% <60
25,00% [60 – 70[
58,33% >70

$\bar{x} = 70{,}9$; s=11,37



Annex 5 – Pharmacy Activity List and Ranking

			Overall Relevance	
Outpatient Care Activities	**Outpatient**	Distribution of Medicine (Front Office)	**4**	
		Inventory Management in Outpatient / Fill presence sheet (Back Office)	**9**	
		Produce Information (Back office)	**14**	→ Intern
		Organize repackaging of outpatient drugs (Back office)	**13**	
		Clinical Trials (Back Office)	**20**	→ Study Coordinador
	Preparation of Custom Medicines	Custom Medicine Preparation (Front Office)	**5**	
		Development of New Custom Medicines (Back Office)	**12**	
		Custom Drugs and Raw Materials Stock Management (Back Office)	**6**	
	Preparation of Cytostatic Drugs and other sterile substances	Preparation of parenteral nutrition, custom and cytostatic medicines (Front Office)	**8**	
		Qualification and control of the working areas (Back Office)	**16**	
		Personnel Training (Back Office)	**11**	
		Monitorization of Instruments and Equipment (Back Office)	**15**	→ Tdt
		Drugs Stock Management and Medical Devices (Back Office)	**10**	→ Tdt
		Clinical Trials (Back Office)	**24**	→ Study Coordinador
General Pharmacy Activities	**Pharmacy Activities**	Reception and Assessment of Orders	**19**	→ Tdt
		Drug Purchase Overview	**4**	
		Warehouse Management	**14**	
		Repackaging of Drugs	**17**	
		Distribution of Drugs	**11**	→ Tdt
		Medical Prescription Validation	**15**	
		Service Consumption Monitorization	**31**	→ Tdt
		Providing information to physicians and nurses about drugs (ex: Compatibility)	**25**	→ Intern

With the aim of performing the economic and financial viability study for other medicines that are not yet included in the pharmaceutical consultation service, a mathematical model was developed. This model is composed of two parts – Collection and Processing of Data & Cost Analysis. The model, which will be subsequently described in further detail, has the medicine **Imatinib** as a practical example, following the suggestion of this being the next medication to be incorporated in the program.

1. Collection and Processing of Data

This first part is executed on Excel Template 01 and must be performed for the **two scenarios, with and without consultation**. It consists in **the aggregation of the data extracted** from the pharmacy database in order to **recreate the history of medicine distribution** for each patient. Such implies, for the scenario **without consultations,** extracting the data for all patients for whom it is **possible to recreate** the history from the **beginning of the prescription**. Regarding the scenario **with consultations**, the extraction of data must occur as soon as the **service is implemented** for all patients **starting a new prescription and at the moment of their first withdrawal**. Although there is the possibility of incorporating pre-existing patients, the data referring to them should be disregarded in order to isolate the results occurring due to the consultation. Additionally the **data consolidation** should be **performed by pathology** to help systematize and execute a more detailed analysis for each medicine.
Through the summary of this data the **Treatment Retention Rates will be computed**, and later on used as inputs in the **cost analysis.**

2. Cost Analysis

The second part of the analysis is performed on Excel Template 02, and will allow for the calculation of the **savings generated** after the implementation of the pharmaceutical consultations. It requires the introduction of the inputs necessary for the execution of the computations: the **different TRRs**. for the two scenarios (with and without consultations); **price of the different lines of treatment** and **number of patients that will be implemented** in the project on an annual basis.
The mathematical model previously described (Ibrutinib case), will estimate how **variations on the TRR** will impact annual medicine spending and **lead to a cost reduction.**

Creation of an Estimation Model

Additionally, an estimation model was created, allowing for different efficiency scenarios of the consultation – effective increase in the number of patients that stays in the first line of treatment – corroborating what was the impact on the TRR and, consequently, how this is translated into cost reductions.
This model is contained in Excel Template 02 and intends to provide a spectre of savings predicted *a priori* for scenarios that the pharmacists consider reasonable, taking into account the installed capacity and resources they have available for the implementation of the project in the ambulatory service of the pharmacy. Moreover, this allows to estimate what will be the costs and benefits for any scenarios they intend to analyse, functioning therefore as a tool to help the decision-making process, by allowing the comparison between different medicines and lines of treatment once the **without consultation** data have been extracted and treated.

Stakeholder	# of people interviewed	Reason Chosen as Relevant Stakeholder
Pharmacy	3	• Pharmacy has the most developed knowledge to the external stakeholders that could influence this project as well as the level of power of the several stakeholders within IPO
Doctors	3	• Doctors are the most critical stakeholder to ensure the functioning and relevance of the pharmaceutical consultations
Nurses	2	• Given their support position to the doctor and their influence on the patient, it is relevant to understand their motivations and worries
Board	1	• Although they have little formal power, they are the main point of contact between IPO and the ACSS, which means their approval will influence the pharmacy's chances of receiving additional funding and personnel.
Patients	-	• Patients are the main beneficiary of Pharmaceutical Consultations, and their main purpose will always be to increase the level of care they receive
Politicians	-	• Politicians have a significant impact on public institutions
ACSS + ARS	-	• The ACSS is ultimately responsible for determining the funding each hospital/department will receive throughout the considered period • The ARS is a more local association, with whom hospitals in the *Lisboa e Vale do Tejo* area tipically negotiate. Only afterwards is funding decided by the ACSS

Power Categories	Doctor	Nurse	Board
Formal – Clinical Decision	H	L	L
Control of Strategic Resources - Hiring	L	L	M
Control of Strategic Resources – Financing	L	L	H
Involvement in Strategic Implementation	H	L	H
Knowledge and Skills	M	L	L

Power Categories	Patient	Political Parties	ACSS + ARS
Ability to mobilize resources	L	M	H
Involvement in Strategy Implementation	H	L	M

Stakeholder	Interests	Type of Interest	Level of Interest	Priority
Doctors	Consultations are benefitial for the patient by increasing their treatment knowledge **(+)** Some doctors may be threatened due to the extension of pharmacist activities **(-)**	+/0	High	1
Patients	Want to receive the best possible level of care as long as the benefits are clear **(+)**	++	High	2
Nurses	Believe the increase in medication monitorization as a benefit for the patient **(+)** Patients may be confused due to the amount of possible overlapping between pharmaceutical and nursing consultations **(-)**	0/-	Low	5
Board	Want the consultations to be expanded as soons as possible as long as the clinical benefits are clinical proven **(+)** Since some patients do not pay attention the doctors consultations, an additional source of countrol is benefitial **(+)** Low number of avaible human resources makes it difficult to expand the pharmaceutical consultations **(-)**	++	High	3
ACSS + ARS	Positive interest due to the expected positive financial returns of the pharmacy consultation **(+)** New line of activity requires additional funding **(-)**	0	Medium	4
Politicians	Only be interested if consultations bring them if there is a high political motivation to increase the number of pharmacists of IPO **(+)**	0	Low	6