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***Ph.D.* - XXV CYCLE**
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PAIN OUT INTERNATIONAL:
Treatment of postoperative pain in Catania's area. Patient's perspective
- *Observational Clinical Study* –

***Ph. D.* Thesis**

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1. INTRODUCTION

1.1 Postoperative pain

Post-operative pain (PP) is an inevitable consequence of surgery. About 234.2 million major surgical procedures are undertaken every year worldwide; more than 40 million patients undergo surgery every year in Europe (about 1 in 18 people) and about 75 million in US [(1)]. Moreover, it is likely that the improvement in early diagnosis and the advances in anaesthesiological and surgical technologies will largely contribute to increase the indications and thus the amount of procedures performed worldwide. Of course the surgical act is meant to provide benefits. Nevertheless, as results of the intervention itself and generally of the hospitalization process, patients are exposed not only to intraoperative risks, but to perioperative events as well, which may even cause death.

Among the perioperative risk factors contributing to mortality and morbidity, PP is well recognized not only as affecting patient's comfort and being a source of distress for families, but is also well known as an important contributor to the onset of metabolic, respiratory, cardiovascular and psychological alterations [(2)]. Some physiological responses to acute pain and stress are mediated by the neuroendocrine system activation and the increased sympathetic tone. As consequence, patients develop tachycardia, increased myocardial oxygen consumption, immunosuppression, hypercoagulability, persistent catabolism and many others metabolic alterations [(3)]. Moreover pain causes functional limitations such as delayed ambulation, impaired pulmonary mechanics and respiratory function [(4)]. The surgical manoeuvres produce tissue and nerve lesions and the mechanical insult triggers a series of local and systemic inflammatory responses. The magnitude and the duration of this stress response are related to the anatomical site and to the extension of damaged tissue, as well as to the pre-existing patient's co-morbidities. By prolonging the stress response, pain can contribute to several of postoperative complications, such as myocardial infarction and pulmonary embolism. Consequently, the modulation of the stress response plays a pivotal role in the recovery process and efforts should be made in order to mitigate it.

Pain definitely worsens the extent and the length of the stress response after surgery and therefore it is not surprising that a poor PP management increases the incidence of complications [(5)]. Moreover, it does increase also the costs of care and can lead to disabling chronic pain [(6-7)]. Hence the importance of an adequate and efficient treatment of PP in order to significantly reduce the onset of complications and the consumption of resources [(8)].

Adequate analgesia has become an even more important outcome with the implementation of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards for pain management, effective since January 2001 [9] Recognition of pain as the fifth vital sign suggests that its management must be assessed regularly during treatment and, when indicated, be addressed in discharge planning, using standardized, internally developed guidelines [10].

On the other side, notwithstanding the strength of this background and regardless the continuous improvement of pharmaceutical strategies and implementation of *ad-hoc* protocols, PP is still under-estimated and under-treated [11].

1.2 The need for a change

The impact of PP is very high for patients and their families as well as for healthcare professionals and the Healthcare Systems worldwide. Clinicians document [12] and patients continue to fear PP [13]. A recent U.S. survey found as many as 40% to 60% of patients experience moderate, severe, or extreme pain [14-15]. Another study of 10,008 patients reported the incidence of severe pain as 5% in the recovery room and 5.3% 24 hours postoperatively [16].

According to the data provided by the IASP (International Association for Study on Pain) more than 50% of patients who undergo a surgical operation complain from moderate to severe level of pain [11]. About 40% of patients in the United States report inadequate pain relief despite receiving treatment [17] and regional, national and Europe-wide surveys have already documented that hospitalized patients receive a suboptimal treatment for pain [18-19].

Although a progressive improvement in staff's knowledge and attitudes, regardless the increasing pharmaceutical strategies and the implementation of *ad-hoc* protocols, and even if routine assessment of pain is becoming a worldwide accepted standard (principally in the United States [20] and in some Western European countries [18, 21]), endpoints such as PP incidence and intensity have not shown to move forward.

The attention offered by the Health Systems towards this issue seems to be variable and generally suboptimal. Even if routine pain documentation is now considered essential for improving quality of pain management and it is recommended by clinical practice guidelines as the '5th vital sign' and used as a quality indicator [9, 22-23], it does not always well correlate with reduction of pain scores [24-25]. This findings support the contention that routine pain assessment alone is not a sufficient tool to improve quality of care and on its own is probably not a valid indicator for quality of pain management.

Therefore, the need to sharpen awareness among Trusts and healthcare professionals is imminent, altogether with the provision of new approaches and protocols, tailored on the specific surgical intervention as well as on patient's characteristics. So, there is a need for a different strategy aiming to establish the best therapeutic alternatives and then making those options easily accessible, e.g. through web based diffusion. Several projects are now creating registries, providing data about national or international management of PP [26]. Transferring data from the clinical practice to a web-based database (thereby forming a medical *registry*) may help providing performance feedbacks. Hopefully, a worldwide *registry* may then favour a continuous upgrading in the management of PP [27].

2. MATERIALS & METHODS

2.1 Pain Out Project

In order to trigger attention on PP and improve patients' postoperative outcome, PAIN-OUT PROJECT - an observational study - has been ideated and funded by the European Union's 7th Framework Program (http://www.pain-out.eu). Its aim is to provide clinicians with evidence-based approaches for the management of pain after surgery [24, 26]. The project is thought to gradually develop into the following three modules:

1. the creation of a Registry for Feedback and Benchmarking,
2. the development of a Clinical Decision Support System,
3. the share of an Electronic Knowledge Library, a friendly-user and easily accessible tool at doctor's hand and patient's bedside.

As soon as the targets of the PAIN-OUT project will be fully accomplished, the impact on the patients' outcome could be outstanding. Ideally, treatment choices will be empowered and disparities in the treatment of PP all over the world will decrease. Pain Out data could also allow the comparison of the quality of PP treatment among different countries and Healthcare Systems as well as an evaluation of the impact of intra-operative techniques and their effect on PP.

The first step of POP has been the development of a preliminary pilot study [24], held between May and October 2008. Fourteen collaborating centres in 13 countries participated and after the analysis of the results, showing the feasibility of international data collection, the official project was inaugurated in the first trimester 2009, with minor changes to the questionnaire (see below) that have been developed in order to make some question clearer (January 2011).

The creation of a database (first module of Pain Out Project) is based on the development of a web-based structure allowing real-time data collection and insertion from the different participating centres. A peculiarity of this project is the shift of the endpoints from clinician's assessment to patient's viewpoint, assessed through an anonymous questionnaire.

For the purpose of the study, data collection consists of the compilation of two separate charts. The first one, entirely filled by the investigator, is shown in *Appendix 1* and contains different sections: screening criteria, patient's demographics and medical history, the surgical procedure performed, information about the pre-medication, the anaesthesia technique, the pain treatment used, both in the operating theatre and afterwards, in the recovery room area (RRA) and in the ward.

The second chart (see *Appendix 2,* in its second and last version) is the anonymous questionnaire, voluntarily completed by the patient on postoperative day 1 and at least 6 hours after return in the ward. Its initial version was updated with minor changes in January 2011 and contains questions exploring the impact of postoperative pain from different points of view and patients are asked to answer giving a score from 0 to 10 to most of the questions (quantitative scale), or simply responding "YES" or "NOT" (qualitative assessment) to the remaining ones. The questionnaire used by the Pain Out study in order to assess outcomes of adult patients related to post-operative pain treatment is based on the recently revised APS's (American Pain Society's) POQ-R (Patient Outcomes Questionnaire-Revised) [(28)].

Initially, PAIN OUT was conceived only for data collection after general surgery and orthopaedics procedures, with selected European centres involved. However, due to the growing interest by other qualified centres and in order to empower the database, a second non EU-funded branch – so called PAIN OUT INTERNATIONAL – was "activated" for those worldwide centres willing to participate, while the original branch is known as PAIN OUT EUROPE. Pain Out International does not have a formal date for its beginning but generally it started in the first half of 2010. The inclusion criteria of the original branch are shown in Table 1. The only difference in the inclusion criteria between the two PAIN OUT stems regards the surgical specialties involved, being no restriction applied for the non-funded PAIN OUT INTERNATIONAL. Nowadays, there are 53 centres collecting data within the PAIN OUT INTERNATIONAL and Catania belongs to this non EU-funded branch of the study. There is no target number for the ongoing worldwide data collection, which will continue throughout.

Orthopaedic or general surgery
Age >18 years
Ability to provide data on post-operative day 1, at least six hours after return in the ward.
Willingness to participate in the survey
Ability to fill in a questionnaire in the local language, unaided

Table 1. Inclusion criteria for PAIN OT EUROPE.

2.2 Catania's Hospitals network

Catania was one of the first centres to join the POI branch of the study, by starting the data collection on the 1st April 2010 with the aim to initiate a long and durative international collaboration as well as allowing a description of the local management of PP, looking for

disparities in the treatment within the territory and for the possibility to determine improvements in the local pharmacological protocol by providing feedbacks.

We preventively planned the first data analysis after 2 years with the data collected till the 31st March 2012, although still continuing the collection of data afterwards. By involving different Trusts in Catania's area we aimed to achieve the recruitment of a fairly high number of cases. In particular we ideally targeted to reach 3000-5000 cases within two years.

After approval of the local Ethic Committee, we started a series of meetings with the aim to provide detailed explanation of the Standard Operating Procedures (SOPs) and to discuss the possible doubts on the way to collect and then correctly insert the data into the database. In those meetings we involved the trainees/residents of the School of Anaesthesia and Intensive Care of the University of Catania, which were in charge of the data collection, and the local supervisors (senior anaesthetists) designated for each one of the Hospitals involved. The principal investigator and his main collaborators were always telephonically contactable for enquiries and uncertainty regarding the data. In turn, a strict contact and e-mail exchange was and still is maintained with the International Manager for any further doubt. The residents' rotation was organized in order to cover the participating Hospitals as much as possible.

We chose to collect data for procedures involving general surgery, orthopaedics, gynaecology and urology. Five Trusts of the city (for a total of 8 Hospitals) eagerly agreed to be involved in the study. The distribution of the participating surgical units among the different Trusts/Hospitals is shown in Table 2. Three of the Trusts involved (Policlinico-Vittorio Emanuele, Garibaldi and Cannizzaro) belong to the Italian National Health System; on the other side, Oncologic Mediterranean Institute (OMI) and Humanitas Institute are both part of the "private" *Italian Healthcare System* (IHS - however often providing care in a regimen of financial convention/agreement with the public IHS).

In case of a decreasing number of trainees available for data collection, the responsibility for their allocation was held by the Principal Investigator and Director of the School of Anaesthesia and Intensive Care himself. We preventively accepted the possibility of suppression of some of the participating Units in the data collection as the number of residents is progressively falling due to decreasing economic resources.

TRUST	General Surgery	Gynaecology	Orthopaedics	Urology
A. POLICLINICO – VITTORIO EMANUELE				
1. Policlinico University Hospital	X	X		X
2. Vittorio Emanuele Hospital	X		X	X
3. Santo Bambino Hospital		X		
B. GARIBALDI				
1. Garibaldi Centro Hospital			X	
2. Garibaldi Nesima Hospital	X			
C. CANNIZZARO		X	X	X
D. HUMANITAS INSTITUTE	X			
E. ONCOLOGIC MEDITERRANEAN INSTITUTE	X			

Table 2. Scheme of the five Trusts (A-E) involved in the collection of data in Catania. In two of these Trusts (Policlinico-Vittorio Emanuele and Garibaldi) more than one hospital contributed to data collection. Each Trust participated by covering one or more surgical specialties as shown in columns.

2.3 Data organization, endpoints and statistical analysis

From a local perspective, the main aim of this observational study is to perform a descriptive analysis of PP treatment in our territory. We realized that a general description of the entire population may have had few interesting conclusions as too many different factors make the population highly inhomogeneous. For this reason, we preventively agreed to focus more deeply on few subgroups selected according to the intervention performed. However, the number of Hospitals involved, the different surgical specialties, the high variability in patients' demographics made difficult to preliminarily set any surgical sub-populations amenable of analysis.

For this reason we subsequently screened our data, both for single surgical interventions (i.e. thyroidectomy or appendicectomy) and for typology of intervention, such as surgery involving a particular anatomical region (i.e. lower limbs surgery or abdominal laparotomy). We preventively chose to analyse only those sub-population that reached at least 100 cases recorded in the database. In case of more than one Hospital contributing to this amount of cases, we deliberately decided to consider valid only the contribution of those centres collecting at least 25 cases.

Of course, we set as endpoints the results of some questions of the anonymous questionnaire (*Appendix 2*). We preventively divided our endpoints in primary, secondary and tertiary as shown in Table n 3.The endpoints were calculated for the entire population and thus for each subgroup. When analyzing subgroups of patients we generally restricted the analysis to the primary and

secondary endpoints. Only in the analysis comparing different hospitals we included the calculation of the score of three tertiary endpoints (use of non pharmacological treatment, information received about PP treatment options and allowance to participate in the decision among these options). We excluded from analysis those patients that responded to less than two primary endpoints of the questionnaire and those ones for which there was no entry regarding both the intra-operative technique and the postoperative drugs given. We found some cases with reported worst pain score lower than the minimum pain and we obviated to this incongruity by inverting those values. Demographic parameters were only considered if thought to be meaningful. Unfortunately, the year of birth is somewhat imprecise as the project is continuing along the years and we do not have at the present time the resources and time to find out the exact age of each patient. Moreover, data were not inserted on the same day of collection, so the calculation of the age would be still inaccurate even if considering it in view of the day when data were inserted on the web-mask. We did not consider patient's weight, because unlikely to influence PP treatment in small subgroup analysis and because the accuracy of patient's weight in the preoperative period could be inaccurate as well.

PRIMARY ENDPOINTS	Value	TERTIARY ENDPOINTS	Value
Worst Pain (P1)	0-10	Feeling anxious (P5a)	0-10
Time spent in Severe Pain (P3)	%	Feeling Helpless (P5b)	0-10
Relief received by treatment (P7)	%	Interference of pain with out of bed activities (P4d)	0-10
Satisfaction about pain management (P11)	0-10	Interference of pain with in bed activities (P4a)	0-10
Wish more pain treatment (P8)	Y/N	Wish less treatment (P15 v1)	Y/N
SECONDARY ENDPOINTS	Value	Interference with staying asleep (P4c)	0-10
Drowsiness (P6b)	0-10	Use of non pharmacological treatment (P12)	Y/N
Itching (P6c)	0-10	Least Pain (P2)	0-10
Nausea (P6a)	0-10	Information about treatment options (P10 v1)	Y/N
Dizziness (P6d)	0-10	Allowed participation on pain treatment option (P10)	0-10
Pain wake up? (P16 v1)	Y/N		

Table 3. Questions considered as possible endpoints of the analysis. In brackets is shown the number of each question as per questionnaire (second and last version, see appendix 2). If specified "v1" the number of the question refers to the first version of the questionnaire (before the update in January 2011) and does not exist anymore in the last version.

The secondary endpoint – Did pain wake you up? – was changed when the questionnaire was updated to the last "version". In particular the variable was changed from a qualitative (Y/N) into a quantitative question (interference of pain on sleep activity, 0/10). This does not allow merging the answers assessing this issue. As most of the cases collected in our centres refer to the "version 1" of the questionnaire, we still preferred to address the impact of pain on the capacity to stay asleep overnight by using the first version and the qualitative measurement – Did pain wake you up? – even if in a slightly reduced sample.

For the purpose of our analysis we preventively considered the following scenarios:

1. comparison among the different centres (for the same surgical procedure and/or typology of intervention);
2. comparison between the Hospitals belonging to the Italian public and the private IHS (general surgery only potentially allowing this analysis);
3. comparison of the influences on endpoints between different intra-operative and/or postoperative drugs used and combination of them;

With regards to the latter point, one of the main aims of this project is to provide a descriptive analysis about the drugs and techniques used for postoperative pain relief in the territory of Catania. Whenever the sample size allowed it, we considered a comparison of the outcomes within subgroups of a population:

a. assessing the impact of wound infiltration with a local anaesthetic;
b. estimating the differences associated to different intraoperative techniques and patient's outcome;
c. evaluating if any post-operative treatment is associated with better results [Non Steroidal Anti-Inflammatory drugs (NSAIDs) only; Opioid, full and/or partial, only; techniques of loco-regional anaesthesia; combination of the previous]

With regards to the intraoperative period, the study design does not allow to discover the timing and purpose of drug administration. This somewhat complicates the analysis especially for fentanyl and morphine, as it remains unclear if those drugs were used for the induction/maintenance of anaesthesia and/or to prevent postoperative pain before recovery. We reasonably assumed that fentanyl has been used for the induction/maintenance of anaesthesia, while morphine has its main role as drug given to prevent postoperative pain after the emergence of anaesthesia. This assumption has been repeatedly confirmed with the centres involved in the study. However, it cannot be denied that few cases may have followed a different approach. Morphine has always been confirmed by the local supervisors (senior anaesthetist) as not used for induction of anaesthesia in all the centres participating to the study. Nevertheless, the same centres confirmed that in some cases a small dose of fentanyl bolus could have been used before the emergence of anaesthesia with the aim to provide postoperative pain relief.

In Catania's Hospitals network, the system of Post-Anaesthesia Care Unit is not well developed. For this reason, we decided to merge the data recorded in the period spent in the RRA with those acquired from the time spent in the ward.

For those drugs available in *per os*, intramuscular (IM) and intravenous (IV) administration, we intentionally did not consider the route of administration, focusing only on the qualitative analysis according to the administration of each drug (1=given; 0=not given; empty data not available). Moreover, the amount of drugs given was not considered because the timing from the end of the surgical procedure would have certainly been different among patients and difficult to assess with precision in our analysis. We considered in our analysis three main classes of drugs: Opioids, Non Steroidal Anti-Inflammatory drugs (NSAIDs, including paracetamol) and Local anaesthetics.

A screening log is not part of Pain Out methods. The data screening and reorganization with the subsequent statistical analysis were performed through SPSS Statistics 19.0 and PRISMA software. The data were downloaded directly from the central database and the International Manager and subsequently the PAIN OUT Publication Board was informed about our ideas for analysis. The Projects for publication have not been forwarded yet to the Publication Board. The normality of quantitative variables was tested by Kolmogorov-Smirnov test. Quantitative variables are expressed as mean ± standard deviation (SD). The differences between groups were assessed by parametric tests (T-student or ANOVA) for variables with normal distribution, while non-parametric tests (Mann-Whitney for two samples and Kruscal-Wallis with Dunn's test for multiple comparisons) were performed in case of non normal distribution. Categorical variables were expressed as frequencies and percentages (%) and they were analyzed using the Chi-square test with Yates correction for the verification of null hypothesis. All tests were two tailed and a $p < 0.05$ was considered statistically significant for all analyses.

3. RESULTS

3.1 General population

Until the 31st March 2012 there were 54 other centres collecting data in the Pain Out Study (from both branch, Europe and International) and the total number of recruited patients at that time was 27727. The total number of patients recruited in Catania in the same frame of 2 years has been 2706, accounting for 9.76% of the overall data. The questionnaire was filled in by 2441 patients (265 missing). The distribution of those patients among the participating Hospitals and surgical specialties is shown in Table 4.

TRUST	General Surgery	Gynaecology	Orthopaedics	Urology	TOTAL
A. POLICLINICO – VITTORIO EMANUELE					***1094***
1. Policlinico University Hospital	79	142		37	(258)
2. Vittorio Emanuele Hospital	385		172	27	(584)
3. Santo Bambino Hospital		252			(252)
B. GARIBALDI					***273***
1. Garibaldi Centro Hospital			120		(120)
2. Garibaldi Nesima Hospital	153				(153)
C. CANNIZZARO		203	227	65	***495***
D. HUMANITAS INSTITUTE	450				***450***
E. ONCOLOGIC MEDITERRANEAN INSTITUTE	129				***129***
TOTAL	***1196***	***597***	***519***	***129***	***2441***

Table 4. Distribution of the questionnaires filled in by patients, among the participating Hospitals and surgical specialties in Catania.

The mean year of birth was 1959, the male gender represents the 28.3% of the entire population and the mean weight was 71.1 Kg. Height was recorded for less than half of the population so we intentionally did not report the average value. The results of the general analysis of the answers to the questionnaire are shown in Table 5.

PRIMARY ENDPOINTS	Mean	TERTIARY ENDPOINTS	Mean
Worst Pain (P1)	5 ± 2,7	Feeling anxious (P5a)	2,25 ± 2,9
Time spent in Severe Pain (P3) %	27,8 ± 23	Feeling Helpless (P5b)	1,29 ± 2,4
Relief received by treatment (P7) %	63 ± 25	Interference of pain with out of bed activities (P4d)	3,78 ± 3,2
Satisfaction about pain management (P11)	7,6 ± 2	Interference of pain with in bed activities (P4a)	3,45 ± 3
Wish more pain treatment (P8) %	18,8	Wish less treatment (P15 v1)	1,4%
SECONDARY ENDPOINTS	**Mean**	Interference with staying asleep (P4c)	2,09 ± 2,8
Drowsiness (P6b)	2,09 ± 2,7	Use of non pharmacological treatment (P12) %	18,5
Itching (P6c)	0,75 ± 1,6	Least Pain (P2)	2,43 ± 2
Nausea (P6a)	1,81 ± 2,6	Information about treatment options (P10 v1) %	45,2
Dizziness (P6d)	1,38 ± 2,2	Allowed participation on pain treatment option (P10)	3,31 ± 3,5
Pain wake up? (P16 v1) %	27,6		

Table 5. Results of the primary, secondary and tertiary endpoints in the overall population of the study in the territory of Catania

The variety of interventions, patients characteristics and intra-operative anaesthetic techniques used does not fit well with a general analysis and thus with the interpretation of the results, perhaps not allowing a lot of conclusions. However, we found several interesting results analysing the general population:

a. The patient controlled analgesia (intravenous or epidural) was never been used in our territory

b. The surgical wound infiltration (which theoretically applies to most of the interventions) was recorded for only 116 patients, 4.3% of the overall population.

c. The most frequently used postoperative drugs for pain relief were five: diclofenac (n=316, 12.9%), ketorolac (n=919, 37.6%), paracetamol (n=814, 33.3%), morphine (n=453, 18.6%) and tramadol (n=524, 21.5%). Local anaesthetics during the period spent in the RRA or in the ward were used in 41 patients only. The qualitative analysis of the use of NSAIDs shows that ketorolac prescription is significantly higher than paracetamol ($p=0.002$) and diclofenac ($p<0.0001$) and that paracetamol is more frequently used than diclofenac ($p<0.0001$). The year of birth of the patients receiving diclofenac (1966 ± 17) was significantly higher than those patients receiving ketorolac (1959 ± 16, $p<0.0001$) or paracetamol (1960 ± 17, $p<0.0001$).

In order to provide more specific findings and description of pain management in our territory, we focused our analysis on those subpopulations of each surgical specialty that provided a minimum amount of cases as per pre-established methods. This approach makes the population a bit more homogeneous for analysis and thus reduces the possible bias.

3.2 General Surgery

Patients undergoing general surgery represent 49% of the entire population and were distributed in five different Hospitals (four Trusts). Among this population we analysed the subgroup of patients undergoing thyroidectomy.

3.2.1 Thyroidectomy

We collected data on 349 surgical patients having a partial or complete excision of the thyroid. This population was distributed among 5 different Hospitals, three of them (two Trusts) belonging to the public IHS and two being part of the private IHS (Table 6). As per methods, we intentionally excluded 22 patients who did not respond to any of the primary endpoints. Policlinico Hospital was deliberately excluded as collecting data on 10 thyroidectomies only. Table 6 also shows the distribution of the remaining 317 patients. Ten patients underwent to unilateral excision of the thyroid gland (OPCODE1C=06.2), while the remaining ones had a complete thyroidectomy (OPCODE1C=06.4). Of this group, 20,6% were male, mean weight was 69,9 ± 13,1 and mean year of birth 1959. The endpoints are shown in Table 7.

ITALIAN HEALTHCARE SYSTEM	N	HOSPITAL	N
Public	168	**Vittorio Emanuele**	126
		Garibaldi Nesima	42
Private	149	**Humanitas Institute**	84
		Oncologic Mediterranean Institute	65
TOTAL	317	**TOTAL**	317

Table 6. Distribution of the thyroidectomies according to the public or private Healthcare System and among Hospitals. Policlinico Hospital was excluded as collecting only 10 cases.

PRIMARY ENDPOINTS	Mean	SECONDARY ENDPOINTS	Mean
Worst Pain (P1)	4,87 ± 2,3	**Drowsiness (P6b)**	2,51 ± 2,9
Time spent in Severe Pain (P3) %	25,5 ± 21	**Itching (P6c)**	0,53 ± 1,3
Relief received by treatment (P7) %	63,6 ± 23	**Nausea (P6a)**	2,28 ± 2,8
Satisfaction about pain management (P11)	7,64 ± 2	**Dizziness (P6d)**	2,28 ± 2,8
Wish more pain treatment (P8) %	12,6	**Pain wake up? (P16 v1) %**	27,5

Table 7. Primary and secondary endpoints in 317 patients undergoing thyroidectomy (expressed as percentage or as mean and standard deviation)

We considered a first-line analysis dividing the patients per hospital (Table 8) and thus per different Healthcare System (public *vs* private IHS, Table 9).

DEMOGRAPHICS	Vittorio Emanuele (N=126) A	Garibaldi Nesima (N=42) B	Humanitas Institute (N=84) C	Oncological Mediterranean Institute (N=65) D	P value	Dunn's or Chi-square test (p value)
Male Sex %	18,3	26,2	20,2	21,9		ns
PRIMARY ENDPOINTS	A	B	C	D		
Worst Pain (P1)	5,25± 2	4,48 ± 2,1	4,96 ± 2,3	4,22 ± 2,7	**0.013**	**A–D <0.05**
Time spent in Severe Pain (P3) %	29,4 ± 19	26 ± 14	21,1 ± 20	23,7 ± 25	**<0.001**	**A–C <0.01** **A–D <0.05**
Relief received by treatment (P7) %	62 ± 17	56,4 ± 26	66,6 ± 25	67,8 ± 26	**0.019**	**ns**
Satisfaction about pain management (P11)	6,81 ± 1,6	8,04 ± 1,29	8,37 ± 2,1	8,16 ± 2,6	**<0.0001**	**A-B <0.001** **A-C <0.001** **A-D <0.001**
Wish more pain treatment (P8) %	16,9	14,3%	7,4%	9,5		ns
SECONDARY ENDPOINTS						
Drowsiness (P6b)	2,16 ± 2,5	0,55 ± 1,3	3,23 ± 3,3	3,56 ± 3	**<0.0001**	**A-B <0.001** **A-D <0.05** **B-C <0.001** **B-D <0.001**
Itching (P6c)	0,94 ± 1,5	0,14 ± 0,6	0,41 ± 1,1	0,13 ± 0,7	**<0.0001**	**A-B <0.001** **A-C <0.001** **A-D <0.001**
Nausea (P6a)	2,48 ± 2,4	1,55 ± 1,8	2,36 ± 3	2,28 ± 3,46	0.059	ns
Dizziness (P6d)	2,1 ± 2,5	0,55 ± 1,2	2,99 ± 3	2,83 ± 3,3	**<0.0001**	**A-B <0.001** **B-C <0.001** **B-D <0.001**
Pain wake up? (P16 v1) %	37,5	7,1	26,8	26,2	**<0.05**	**A-B <0.001** **B-C <0.05** **B-D <0.05**
TERTIARY ENDPOINTS						
Information about treatment options (P10 v1) %	57,9	45,2	42	26,2		**A-C <0.05** **A-D <0.0005**
Allowed participation on treatment option (P10)	3,96 ± 2,6	3,69 ± 3,3	3,8 ± 3,6	2,9 ± 3,9	**0.054**	**A-D <0.05**
Use of non pharmacological treatment (P12) %	11,9	9,5	16,3	37,7		**A-D <0.0005** **B-D <0.05** **C-D <0.01**

Table 8. Demographics, primary, secondary and three tertiary endpoints in patients undergoing thyroidectomy divided per Hospital. Hospitals are also indicated with letters A to D for the multiple comparisons through the Dunn's and Chi-square with Yates correction test. The p values for multiple comparison are shown only when significantly different.

DEMOGRAPHICS	Public Healthcare System (N=168)	Private Healthcare System (N=149)	p value
Male Sex %	20,2	20,9	0.99
PRIMARY ENDPOINTS			
Worst Pain (P1)	5,06 ± 2	4,65 ± 2,5	0.091
Time spent in Severe Pain (P3) %	28,5 ± 18	22,2 ± 23	**<0.0001**
Relief received by treatment (P7) %	60,6 ± 20	67,1 ± 25	**0.0028**
Satisfaction about pain management (P11)	7,12 ± 1,6	8,28 ± 2,3	**<0.0001**
Wish more pain treatment (P8) %	16,3	8,3	0.053
SECONDARY ENDPOINTS			
Drowsiness (P6b)	1,76 ± 2,4	3,37 ± 3,2	**<0.0001**
Itching (P6c)	0,74 ± 1,4	0,29 ± 1	**0.0003**
Nausea (P6a)	2,24 ± 2,3	2,33 ± 3,2	0.11
Dizziness (P6d)	1,71 ± 2,4	2,92 ± 3,1	**0.0017**
Pain wake up? (P16 v1) %	28,3	26,5	0.86
TERTIARY ENDPOINTS			
Information about treatment options (P10 v1) %	54,8	35,2	**<0.001**
Allowed participation on treatment option (P10)	3,84 ± 2,8	3,42 ± 3,7	0.057
Use of non pharmacological treatment (P12) %	11,3	25,5	**0.002**

Table 9. Demographics, primary, secondary and three tertiary endpoints in patients undergoing thyroidectomy divided according to the Italian Healthcare System, public or private. Mann-Whitney or Chi-square (with Yates correction) test performed and p values are shown in the last column.

With regards to the intraoperative technique, all the cases were performed under general anaesthesia. In 208 interventions (65,6%), remifentanil i.v. was used intraoperatively. Table 10 shows the results of subgroups analysis according to whether remifentanil was used or not for intraoperative anaesthesia.

DEMOGRAPHICS	Use of Remifentanil (N=208)	Remifentanil not used (N=109)	p value
Male Sex %	19,2	23,1	0.50
PRIMARY ENDPOINTS			
Worst Pain (P1)	5,14 ± 2,1	4,34 ± 2,1	**0.002**
Time spent in Severe Pain (P3) %	25,9 ± 20	24,8 ± 21	0.47
Relief received by treatment (P7) %	63,9 ± 21	62,9 ± 26	0.79
Satisfaction about pain management (P11)	7,42 ± 2	8,1 ± 2,1	**0.0004**
Wish more pain treatment (P8) %	13,3	11,2	0.73
SECONDARY ENDPOINTS			
Drowsiness (P6b)	2,63 ± 2,9	2,26 ± 2,9	0.14
Itching (P6c)	0,74 ± 1,4	0,12 ± 0,7	**<0.0001**
Nausea (P6a)	2,46 ± 2,7	1,94 ± 2,9	**0.009**
Dizziness (P6d)	2,52 ± 2,8	1,81 ± 2,7	**0.0032**
Pain wake up? (P16 v1) %	33,6	18,4	**0.012**

Table 10. Demographics, primary and secondary endpoints in patients undergoing thyroidectomy divided according to the use of intraoperative remifentanil. Mann-Whitney or Chi-square (with Yates correction) test performed and p values are shown in the last column.

The analysis of the intraoperative drugs administration is shown in Table 11. For those patients not receiving remifentanil, fentanyl was administered in all cases. For the reason discussed in the material and methods, since fentanyl was assumed as not given intraoperatively for postoperative pain relief, the analysis was not performed. The group of patients receiving remifentanil had a significantly higher intraoperative use of NSAIDs ($p<0.0001$). Of the 9 patients receiving morphine in the remifentanil group, 8 had tramadol as well, while morphine was never used in combination with tramadol in the non-remifentanil group. The analysis regarding the administration of *non-remifentanil/non-fentanyl* opioids for pain relief shows a significantly higher use in the remifentanil group (n=184/208 vs n=38/109, $p<0.001$).

INTRAOPERATIVE DRUG ADMINISTRATION	Use of Remifentanil (N=208)	Remifentanil Not used (N=109)	Chi square test
Fentanyl (N=276)	167	109	**NA**
Morphine (N=11)	9 (4%)	2 (2%)	p=0.41
Tramadol (N=219)	183 (88%)	36 (33%)	**p<0.001**
Paracetamol (N=92)	55 (26%)	37 (34%)	p=0.20
Diclofenac (N=2)	2 (1%)	0	p=0.78
Ketorolac (N=241)	175 (84%)	66 (61%)	**p<0.001**

Table 11. Analysis of the intraoperative Opioids and Non Steroidal Anti-Inflammatory Drugs given in two subpopulations: those receiving anaesthesia with remifentanil and those not. Chi-square test (with Yates correction) is shown in the last column.
NA = Not assessed by statistical analysis

For what concerns the postoperative period, the data regarding the administered drugs for pain relief were not available for 89 patients (28% of the subgroup of thyroidectomy). At least one NSAID (diclofenac, ketorolac, paracetamol) was administered to 131 patients of the remifentanil group (63%) and to 68 of the non-remifentanil group (62.4%, $p=0.99$). An opioid drug (morphine and/or tramadol) was administered to 63 patients of the remifentanil group (30.3%) and to 50 of the non-remifentanil group (45.9%, $p=0.009$). The differences in the use of each postoperative drug among the two subpopulations are shown in Table 12.

POSTOPERATIVE DRUG ADMINISTRATION	Use of Remifentanil (N=208)	Remifentanil Not used (N=109)	Chi square test
Morphine (N=11)	3 (1%)	8 (7%)	**p=0.016**
Tramadol (N=103)	60 (29%)	43 (39%)	p=0.073
Paracetamol (N=72)	43 (21%)	29 (27%)	p=0.29
Ketorolac (N=125)	79 (38%)	46 (42%)	p=0.54
Diclofenac (N=19)	19 (9%)	0	**p=0.003**

Table 12. Analysis of the postoperative use of Opioid and Non Steroidal Anti-Inflammatory Drugs in two subpopulations of patients undergoing thyroidectomy: those receiving anaesthesia with remifentanil and those not. Chi-square test (with Yates correction) is shown in the last column.

We have records of 308 patients regarding the use of non-pharmacological methods for PP relief. Table 13 shows the differences.

DEMOGRAPHICS	Non-pharmacological methods not used (N=254)	Use of non-pharmacological methods (N=54)	p value
Male Sex %	22	11,5	0.10
PRIMARY ENDPOINTS			
Worst Pain (P1)	4,7 ± 2,2	5,69 ± 2,4	**0.0017**
Time spent in Severe Pain (P3) %	24,4 ± 18	31,3 ± 27	0.17
Relief received by treatment (P7) %	64,4 ± 22	58,8 ± 24	0.12
Satisfaction about pain management (P11)	7,65 ± 2	7,57 ± 2,1	0.68
Wish more pain treatment (P8) %	12	13,7	0.73
SECONDARY ENDPOINTS			
Drowsiness (P6b)	2,2 ± 2,8	3,59 ± 2,9	**0.0004**
Itching (P6c)	0,56 ± 1,3	0,44 ± 1,1	0.50
Nausea (P6a)	2,34 ± 2,7	1,93 ± 2,8	0.15
Dizziness (P6d)	2,13 ± 2,8	2,64 ± 2,6	0.093
Pain wake up? (P16 v1) %	23,8	47,4	**0.0028**

Table 13. Demographics, primary and secondary endpoints in patients undergoing thyroidectomy divided according to the use of non-pharmacological methods for postoperative pain relief. Mann-Whitney or Chi-square (with Yates correction) test performed and p values shown in the last column.

The wound was infiltrated in only 3 patients, thus not allowing further analysis.

3.3 *Gynaecology*

Gynaecological patients represent 24.4% of the entire population and were distributed in three different Hospitals (two Trusts; Table 2). Among this group of surgical patients we analysed the following populations: 1) Hysterectomies and other uterine procedures (open abdominal surgery); 2) Caesarean Sections.

3.3.1 Hysterectomies and other uterine procedures (open abdominal surgery)

We collected data on 214 gynaecological patients undergoing open abdominal procedure involving a partial or total excision of the uterus (OPCODE1C = 68.29, 68.3, 68.4, 68.6). Thirteen patients did not fill in the questionnaire and were removed from analysis as well as 2 patients for which there was no information about intra-operative technique and postoperative drugs used. The remaining population was distributed among 6 Hospitals (Table 14). As per methods, we deliberately excluded a total of 19 patients recruited in centres not achieving the established cut-off (n≥25). Of the residual 180, we also intentionally excluded 5 patients receiving intraoperative regional anaesthesia (without any general anaesthesia) in order to analyze a more homogeneous sample. The type of intervention performed in the remaining 175 cases is shown in Table 15.

HOSPITAL	N
Vittorio Emanuele	2
S. Bambino	**34**
Policlinico	**53**
Cannizzaro	**93**
Humanitas	16
Oncologic Mediterranean Institute	1
TOTAL	**199**

Table 14. Distribution of the open abdominal uterine surgery among the Hospitals collecting data.

OPCODE1C	Type of Surgery	N
68.29	**Other excision or destruction of lesion of uterus - Uterine myomectomy**	42
68.3	**Subtotal Hysterectomy**	6
68.4	**Total abdominal hysterectomy**	89
68.6	**Radical abdominal hysterectomy**	38
	TOTAL	175

Table 15. Distribution of the analyzed sample according to the open abdominal uterine surgery performed

The mean weight is 67,5 ± 13,2 Kg and mean year of birth 1962 ± 11. The endpoints are shown in Table 16.

PRIMARY ENDPOINTS	Mean	SECONDARY ENDPOINTS	Mean
Worst Pain (P1)	6,15 ± 2,9	**Drowsiness (P6b)**	3,05 ± 3,3
Time spent in Severe Pain (P3) %	38,8 ± 28	**Itching (P6c)**	0,59 ± 1,4
Relief received by treatment (P7) %	62,3 ± 25	**Nausea (P6a)**	3,05 ± 3,3
Satisfaction about pain management (P11)	7,42 ± 2,3	**Dizziness (P6d)**	1,57 ± 2,5
Wish more pain treatment (P8) %	32,4	**Pain wake up? (P16 v1)** %	43

Table 16. Primary and secondary endpoints in 175 patients undergoing open uterine surgery under general anaesthesia.

We considered a first-line analysis dividing the patients per hospital (Table 17).

PRIMARY ENDPOINTS	Cannizzaro (N=94) A	Policlinico (N=53) B	S. Bambino (N=29) C	P value	Dunn's or Chi-square test (p value)
Worst Pain (P1)	6,55 ± 2,7	6,66 ± 3,2	3,97 ± 2	**p<0.0001**	**A-C <0.0001** **B-C <0.0001**
Time spent in Severe Pain (P3) %	42,3 ± 28	41,5 ± 32	22,8 ± 18	**0.005**	**A-C <0.01** **B-C <0.05**
Relief received by treatment (P7) %	58,5 ± 26	68,9 ± 23	61,7 ± 20	0.062	ns
Satisfaction about pain management (P11)	6,95 ± 2,5	8,4 ± 1,9	7,14 ± 1,5	**0.0003**	**A-B <0.0001** **B-C <0.01**
Wish more pain treatment (P8) %	42,4	18,9	25		**A-B <0.01**
SECONDARY ENDPOINTS	**A**	**B**	**C**		
Drowsiness (P6b)	3,29 ± 3,1	3,91 ± 3,7	0,76 ± 1,41	**0.0002**	**A-C <0.0001** **B-C <0.0001**
Itching (P6c)	0,35 ± 1,2	0,26 ± 0,8	1,93 ± 2,2	**p<0.0001**	**A-C <0.0001** **B-C <0.0001**
Nausea (P6a)	2,72 ± 3,4	3,89 ± 3,6	2,55 ± 2	0.091	ns
Dizziness (P6d)	1,62 ± 2,5	1,92 ± 2,9	0,76 ± 1,46	0.21	ns
Pain wake up? (P16 v1) %	59,8	35,5	3,4		**A-B <0.05** **A-C <0.0001** **B-C <0.01**
TERTIARY ENDPOINTS	**A**	**B**	**C**		
Information about treatment options (P10 v1) %	16,1	45,3	44,8		**A-B <0.0005** **A-C <0.005**
Allowed participation on treatment option (P10)	1,32 ± 2,8	3,81 ± 3,9	2,14 ± 2,9	**p<0.0001**	**A-B <0.0001**
Use of non pharmacological treatment (P12) %	20,4	17	13,8		ns

Table 17. Primary, secondary and three of the tertiary endpoints in patients undergoing open abdominal uterine surgery divided per Hospital. Hospitals are also indicated with letters A to C for the multiple comparisons through the Dunn's and Chi-square tests with Yates correction. The p values for multiple comparisons are shown only when significantly different.

In order to understand the differences among the hospital we considered again to screen the population according to the intraoperative use of remifentanil (Table 18). We detected 47 patients with documented use of remifentanil (26,9%) and 128 without it (73,1%). Table 19 shows the drugs administered during the intraoperative period for postoperative pain relief. Again, as per methods, fentanyl analysis was not performed.

PRIMARY ENDPOINTS	Use of Remifentanil (N=47)	Remifentanil not used (N=128)	p value
Worst Pain (P1)	7,11 ± 2,3	5,82 ± 3	**0.019**
Time spent in Severe Pain (P3) %	46,3 ± 32	36,3 ± 27	0.073
Relief received by treatment (P7) %	59,6 ± 28	63 ± 24	0.60
Satisfaction about pain management (P11)	7,27 ± 2,3	7,46 ± 2,2	0.62
Wish more pain treatment (P8) %	39,1	30,7	0.39
SECONDARY ENDPOINTS			
Drowsiness (P6b)	4,13 ± 3,2	2,62 ± 3,2	**0.004**
Itching (P6c)	0,53 ± 1,6	0,61 ± 1,4	0.60
Nausea (P6a)	4,13 ± 3,9	2,58 ± 2,9	**0.03**
Dizziness (P6d)	2,23 ± 2,8	1,31 ± 2,4	**0.002**
Pain wake up? (P16 v1) %	63,2	36,2	**0.007**

Table 18. Primary and secondary endpoints in patients undergoing open abdominal uterine surgery divided according to the use of intraoperative remifentanil. Mann-Whitney or Chi-square (with Yates correction) test performed and p values are shown in the last column.

Among the group treated with remifentanil, one patient received both morphine and tramadol intraoperatively. The comparison regarding the intraoperative use of non-remifentanil/non-fentanyl opioids showed a trend towards lower use in the remifentanil group if compared with patients not receiving remifentanil (n=27/47 *vs* n=94/128, p=0.065). This result seems to be driven by the larger use of tramadol in the non-remifentanil group. Four patients in the remifentanil group and 9 in the non remifentanil group received both ketorolac and paracetamol and there was no difference in intraoperative NSAIDs use among the two groups (respectively, n=33/47 *vs* n=97/128, p=0.58).

INTRAOPERATIVE DRUG ADMINISTRATION	Use of Remifentanil (N=47)	Remifentanil not used (N=128)	Chi square test
Fentanyl (N=128)	8 (17%)	120 (94%)	**NA**
Morphine (N=80)	23 (49%)	57 (45%)	p=0.73
Tramadol (N=42)	5 (11%)	37 (29%)	**p=0.02**
Paracetamol (N=100)	25 (53%)	75 (59%)	P=0.64
Ketorolac (N=43)	12 (26%)	31 (24%)	P=0.98

Table 19. Analysis of the intraoperative use of Opioids and Non Steroidal Anti-Inflammatory Drugs in two subpopulations: those receiving anaesthesia with remifentanil and those not. Chi-square test (with Yates correction) is shown in the last column.
NA = Not assessed by statistical analysis

Considering again the two groups of patients receiving or not remifentanil, the analysis of the drugs used for postoperative pain relief is shown in Table 20. Two patients in the remifentanil group and one in the non-remifentanil group received both morphine and tramadol; there was no difference in opioid use in the postoperative period among the two groups (respectively, n=34/47 *vs* n=92/128, p=0.88). In three cases of the remifentanil group and 16 of the non-remifentanil group a combination of different NSAIDs was used in the postoperative period, showing a trend towards higher NSAIDs use in the non-remifentanil group (respectively, n=30/47 *vs* n=99/128, p=0.11).

POSTOPERATIVE DRUG ADMINISTRATION	Use of Remifentanil (N=47)	Remifentanil not used (N=128)	Chi square test
Morphine (N=71)	23 (49%)	48 (37%)	p=0.23
Tramadol (N=58)	13 (28%)	45 (36%)	p=0.45
Paracetamol (N=62)	15 (32%)	47 (37%)	p=0.68
Ketorolac (N=58)	14 (30%)	44 (34%)	p=0.70
Diclofenac (N=29)	4 (9%)	25 (20%)	p=0.13

Table 20 Analysis of the postoperative use of Opioids and Non Steroidal Anti-Inflammatory Drugs in two subpopulations: those receiving anaesthesia with remifentanil and those not. Chi-square test (with Yates correction) is shown on the last column.

The wound was infiltrated in only 3 patients, thus not allowing further analysis.

Regardless of the intraoperative technique, we have evidence of pain treatment for 166 patients (94.9%) during the period spent in the RRA and in the ward. In 9 cases (5.1%) the information on the postoperative period were not available. One patient received postoperative treatment with epidural analgesia and was excluded from the analysis. Of the remaining 165, we found a total of 87 patients (52.7%) receiving a combination of Opioid and NSAIDs for postoperative pain treatment. An opioid-only based postoperative analgesia was used in 36 patients (21.8%) and NSAIDs-only approach was recorded for 42 patients (25.5%). The results of primary and secondary endpoints among these three groups are shown in Table 21.

The wound was infiltrated in only 3 patients thus not warranting any further analysis.

PRIMARY ENDPOINTS	Opioid + NSAIDS (N=87) A	Opioid only (N=36) B	NSAIDs only (N=42) C	P value	Dunn's or Chi-square test (p value)
Worst Pain (P1)	5,42 ± 2,8	6,77 ± 2,9	6,81 ± 2,9	**0.006**	**A-B <0.05** **A-C <0.05**
Time spent in Severe Pain (P3) %	32,4 ± 26	42,1 ± 31	44,3 ± 28,6	0.053	ns
Relief received by treatment (P7) %	66,6 ± 23	58,3 ± 26	58,7 ± 24	0.10	ns
Satisfaction about pain management (P11)	7,93 ± 1,9	7,11 ± 2,4	6,83 ± 2,6	**0.046**	ns
Wish more pain treatment (P8) %	20,9	50	38,1		**A-B <0.005** A-C 0.06
SECONDARY ENDPOINTS	**A**	**B**	**C**		
Drowsiness (P6b)	2,94 ± 3,2	3,44 ± 3,5	2,74 ± 3,2	0.69	ns
Itching (P6c)	0,78 ± 1,7	0,44 ± 1	0,33 ± 1	0.32	ns
Nausea (P6a)	2,78 ± 3,3	3,17 ± 3,3	2,79 ± 3,1	0.84	ns
Dizziness (P6d)	1,36 ± 2,3	2 ± 3	1,27 ± 2	0.62	ns
Pain wake up? (P16 v1) %	39,7	47,8	39,5		ns

Table 21. Primary and secondary endpoints in patients undergoing open abdominal uterine surgery divided according to the postoperative use of opioids and/or Non Steroidal Anti-Inflammatory Drugs (NSAIDs) for pain relief. Groups are also indicated with letters A to C for the multiple comparisons through the Dunn's and Chi-square (with Yates correction) tests. The p values for multiple comparisons are shown only when significantly different.

3.3.2 Caesarean Section (CS)

We collected data and questionnaire of 146 classical CS (OPCODE1C = 74.0), 144 of them belonging to the same Hospital (S. Bambino) and 2 collected in Cannizzaro Hospital. As per general method of the analysis, we intentionally excluded the latter 2 cases. The mean year of birth in this population is 1979, and mean weight is 79.5 Kg. Table 22 shows the results of the questionnaire for primary and secondary endpoints.

PRIMARY ENDPOINTS	Mean	SECONDARY ENDPOINTS	Mean
Worst Pain (P1)	**3,89 ± 1,9**	**Drowsiness (P6b)**	**0,4 ± 1**
Time spent in Severe Pain (P3) %	**19,5 ± 14**	**Itching (P6c)**	**1,61 ± 2,1**
Relief received by treatment (P7) %	**66,4 ± 23**	**Nausea (P6a)**	**1,49 ± 1,8**
Satisfaction about pain management (P11)	**7,6 ± 1,6**	**Dizziness (P6d)**	**0,4 ± 1,1**
Wish more pain treatment (P8) %	**9**	**Pain wake up? (P16 v1)** %	**7**

Table 22. Primary and secondary endpoints of patients undergoing caesarean section in S. Bambino Hospital

The intraoperative technique used was always a regional anaesthesia with central nerve block (likely spinal) and the different pharmacological combinations used are shown in Table 23. In 4 cases the local anaesthetic drugs used were not reported, despite we have evidence of 3 of these patients receiving an opioid administration for regional anaesthesia (morphine, n=2; fentanyl, n=1). For one patient both Bupivacaine and Levo-Bupivacaine were recorded as intraoperative drugs administered in regional anaesthesia (with morphine) associated to a subcutaneous wound infiltration. In this last case it is not possible to find out which local anaesthetic was used for anaesthesia and which one for wound infiltration.

Drug used for spinal anaesthesia	N
Bupivacaine only	1
Bupivacaine + Morphine	**100**
Bupivacaine + Fentanyl	**32**
Levo-Bupivacaine + Fentanyl	6
Unclear	5
Total	**144**

Table 23. Drugs used in spinal anaesthesia for caesarean section.

We compared the outcomes between the two more representative groups in which Bupivacaine was used with the adjunct of morphine or fentanyl. The results did not show any difference in the endpoints (Table 24).

PRIMARY ENDPOINTS	Bupivacaine + Morphine (N=100)	Bupivacaine + Fentanyl (N=32)	p value
Worst Pain (P1)	3,87 ± 1,9	4,16 ± 2	0.35
Time spent in Severe Pain (P3) %	18,6 ± 15	22,2 ± 14	0.13
Relief received by treatment (P7) %	68,2 ± 23	63,7 ± 22	0.22
Satisfaction about pain management (P11)	7,65 ± 1,6	7,47 ± 1,6	0.46
Wish more pain treatment (P8) %	9	12,5	0.57
SECONDARY ENDPOINTS			
Drowsiness (P6b)	0,4 ± 1	0,37 ± 0,8	0.84
Itching (P6c)	1,74 ± 2,3	1,41 ± 1,7	0.91
Nausea (P6a)	1,37 ± 1,8	1,78 ± 1,9	0.27
Dizziness (P6d)	0,36 ± 1	0,56 ± 1,3	0.43
Pain wake up? (P16 v1) %	7,7	9,4	0.67

Table 24. Primary and secondary endpoints within the two subgroups of caesarean sections, according to the intraoperative drugs used for spinal anaesthesia. Mann-Whitney or Chi-square (with Yates correction) test performed and p values are shown in the last column.

The qualitative analysis of the drugs used for pain relief during the postoperative period has shown some difference between the patients receiving intrathecal morphine or fentanyl. We performed this analysis in the two groups in Table 24 (bupivacaine-morphine and bupivacaine-fentanyl) and the results are shown in Table 25. There was a significantly higher number of patients in the group of intrathecal bupivacaine-fentanyl receiving a postoperative opioid administration (n=25/32 *vs* n=6/100, p<0.001). On the other side there was no differences in the patients treated with postoperative NSAIDs (n=99/100 *vs* n=31/32, p=0.98) Twenty-three patients in the group of bupivacaine-morphine were treated with only one drug for pain relief (23%) while only 6% (n=2/32) of those receiving bupivacaine-fentanyl had only one drug for pain relief (p=0.065). The use of non-pharmacological tools for pain relief was not different between the two groups (bupivacaine-morphine = 23% *vs* bupivacaine-fentanyl = 26%, p=0.93).

POSTOPERATIVE DRUG ADMINISTRATION	Bupivacaine + Morphine (N=100)	Bupivacaine + Fentanyl (N=32)	Chi square
Morphine (N=1)	**1 (1%)**	**0**	p=0.56
Tramadol (N=30)	**5 (5%)**	**25 (78%)**	**p=<0.001**
Diclofenac (N=95)	**87 (87%)**	**8 (25%)**	**p=<0.001**
Paracetamol (N=108)	**78 (78%)**	**30 (94%)**	p=0.08
Ketorolac (N=5)	**4 (4%)**	**1 (3%)**	p=0.76

Table 25. Postoperative drug administration for pain relief in the two subgroups of caesarean sections, according to the intra-operative drugs used for spinal anaesthesia. Chi-square test (with Yates correction) is shown in the last column.

When extending the analysis to all the patients receiving intrathecal morphine or fentanyl (regardless of the local anaesthetic used), so adding 10 more patients (3 in the morphine group and 7 in the fentanyl group), we did not find any significant change of results compared with those shown in Table 25.

The surgical wound was infiltrated in 26 patients (18%) and the analysis of this subgroup compared to the one not receiving infiltration with local anaesthetic shows some significant differences (Table 26).

PRIMARY ENDPOINTS	Wound Infiltration (N=26)	No wound infiltration (N=118)	p value
Worst Pain (P1)	4,27 ± 1,3	3,81 ± 2	0.34
Time spent in Severe Pain (P3) %	26,6 ± 14	18 ± 14	**0.0033**
Relief received by treatment (P7) %	51,6 ± 23	69,7 ± 22	**0.0005**
Satisfaction about pain management (P11)	7,5 ± 1,1	7,62 ± 1,6	0.45
Wish more pain treatment (P8) %	7,7	9,3	0.79
SECONDARY ENDPOINTS			
Drowsiness (P6b)	0,54 ± 1,1	0,37 ± 1	0.58
Itching (P6c)	2,31 ± 1,9	1,46 ± 2,1	**0.021**
Nausea (P6a)	1,5 ± 1,5	1,49 ± 1,9	0.69
Dizziness (P6d)	0,35 ± 1	0,41 ± 1,1	0.84
Pain wake up? (P16 v1)	0	8,5	0.26

Table 26 Primary and secondary endpoints in the two subgroups of caesarean sections, according to the infiltration (single shot) of the surgical wound with local anaesthetics. Mann-Whitney or Chi-square (with Yates correction) test performed and p values shown in the last column.

Table 27 shows the combination of Opioids and NSAIDs used in the postoperative period for pain relief. For two patients there was no information available regarding the postoperative analgesia. Of those one-hundred and forty patients receiving NSAIDs during the postoperative period, 36 were treated with an opioid as well.

NSAIDS	OPIOID	
N	Y	2
Y	Y	36
Y	N	104
N	N	2
		144

Table 27 Postoperative combination of Opioids and NSAIDs used in the for pain relief after caesarean section.

We compared the group of patients receiving NSAIDs only with those receiving a combination of NSAIDs and Opioid medication (Table 28).

PRIMARY ENDPOINTS	NSAIDs and Opioid (N=36)	NSAIDs only (N=104)	p value
Worst Pain (P1)	3,91 ± 1,7	3,87 ± 2	0.69
Time spent in Severe Pain (P3) %	21,9 ± 12	18,5 ± 15	0.11
Relief received by treatment (P7) %	59,7 ± 23	68,6 ± 23	**0.036**
Satisfaction about pain management (P11)	7,44 ± 1,6	7,65 ± 1,5	0.42
Wish more pain treatment (P8) %	11,1	7,7	0.66
SECONDARY ENDPOINTS			
Drowsiness (P6b)	0,44 ± 1,2	0,39 ± 1	0.41
Itching (P6c)	1,39 ± 2,1	1,70 ± 2,1	0.49
Nausea (P6a)	1,47 ± 1,7	1,49 ± 1,8	0.89
Dizziness (P6d)	0,5 ± 1,3	0,37 ± 1	0.86
Pain wake up? (P16 v1) %	8,3	6,8	0.95

Table 28. Primary and secondary endpoints in the two subgroups of caesarean sections, according to the postoperative treatment. NSAIDs = Non-Steroidal Anti-Inflammatory Drugs.

Thirty-two patients used of non-pharmacological methods for pain relief (cooling, 100%), six did not specify and 107 did not use non-pharmacological methods. By analysing the endpoints among those patients using or not non-pharmacological methods, we did not find any significant differences (Table 29). The percentages of patients receiving Opioids and/or NSAIDs are not different among these two groups.

PRIMARY ENDPOINTS	Non-pharmacological methods not used (N=107)	Use of non-pharmacological methods (N=32)	p value
Worst Pain (P1)	3,77 ± 2	4,5 ± 1,3	**0.053**
Time spent in Severe Pain (P3) %	17,9 ± 14	25,9 ± 15	**0.003**
Relief received by treatment (P7) %	70,2 ± 22	50,9 ± 22	**<0.0001**
Satisfaction about pain management (P11)	7,59 ± 1,6	7,42 ± 1,2	0.32
Wish more pain treatment (P8) %	8,4	12,5	0.73
SECONDARY ENDPOINTS			
Drowsiness (P6b)	0,32 ± 0,8	0,75 ± 1,6	**0.18**
Itching (P6c)	1,39 ± 1,9	2,59 ± 2,5	**0.012**
Nausea (P6a)	1,53 ± 1,8	1,5 ± 2	0.80
Dizziness (P6d)	0.35 ± 1	0,62 ±1,3	0.18
Pain wake up? (P16 v1) %	9,4	0	0.16

Table 29. Primary and secondary endpoints in the two subgroups of caesarean sections, using or not non-pharmacological methods as adjuncts for pain relief.

3.4 *Orthopaedics*

Data on patients undergoing orthopaedic procedures were recorded in three Hospitals (Vittorio Emanuele, Garibaldi Centro and Cannizzaro) and represent 21.3% of the entire Pain Out data collected. Among this group we did not find any surgical population with the target of 100 interventions. However we decided to analyze the subgroup of patients undergoing an open procedure involving the hip or the lower limb (excluding the ankle and the foot).

3.4.1 Hip and lower limb orthopaedic surgery

We included in this subgroup only those interventions involving an internal fixation of fracture or a joint replacement/revision (hip or knee). Those receiving an open reduction of fracture without internal fixation were excluded as well as those cases where the anatomical region involved was not specified. Foot and ankle were excluded as deemed to be exposed to interventions with lower predicted postoperative pain.

According to the ICD-9 we collected data of patients recorded with the following OPCODE1C: 79.35, 79.36, 81.51, 81.52, 81.53, 81.54, 81.55. The number and type of intervention per Hospital are reported in Table 30.

OPCODE1C	Type of Surgery	Vittorio Emanuele	Garibaldi Centro	Cannizzaro	N
79.35	**Femoral Open reduction of fracture with internal fixation**	8	12	10	**30**
79.36	**Tibial and/or fibular Open reduction of fracture with internal fixation**	29	10	13	**52**
81.51	**Total hip replacement**	9	18	12	**39**
81.52	**Partial hip replacement**	1	0	0	**1**
81.53	**Revision of hip replacement**	1	0	3	**4**
81.54	**Total knee replacement**	14	10	2	**26**
81.55	**Revision of knee replacement**	2	1	0	**3**
TOTAL		**64**	**51**	**40**	**155**

Table 30. Distribution of data among the Hospitals according to type of orthopaedic surgery (involving hip or lower limb).

The mean year of birth is 1952, 48% are male and mean weight is 78 Kg. Table 31 shows the results of the questionnaire for primary and secondary endpoints.

PRIMARY ENDPOINTS	Mean	SECONDARY ENDPOINTS	Mean
Worst Pain (P1)	5.57 ± 2,8	**Drowsiness (P6b)**	1,95 ± 2,6
Time spent in Severe Pain (P3) %	34,1 ± 25	**Itching (P6c)**	0,87 ± 1,9
Relief received by treatment (P7) %	64,6 ± 25	**Nausea (P6a)**	2,28 ± 2,8
Satisfaction about pain management (P11)	7,37 ± 2,2	**Dizziness (P6d)**	1,29 ± 2,4
Wish more pain treatment (P8) %	28,6	**Pain wake up? (P16 v1)** %	41,8

Table 31. Primary and secondary endpoints in 155 patients undergoing orthopaedic surgery (involving hip or lower limb).

We then considered a first-line analysis dividing the patients per hospital (Table 32).

DEMOGRAPHICS	Vittorio Emanuele (N=64) A	Garibaldi Centro (N=51) B	Cannizzaro (N=40) C	P value	Dunn's or Chi-square test (p value)
Male sex %	44,2	51	50		ns
PRIMARY ENDPOINTS	**A**	**B**	**C**		
Worst Pain (P1)	4,94 ± 2,8	5,55 ± 2,8	6,64 ± 2,5	**0.009**	**A-C <0.01**
Time spent in Severe Pain (P3) %	26,6 ± 22	33,3 ± 25	47,9 ± 26	**0.0002**	**A-C <0.001** **B-C <0.05**
Relief received by treatment (P7) %	66,2 ± 24	65,9 ± 26	60 ± 26	0.41	ns
Satisfaction about pain management (P11)	7,7 ± 2	7,43 ± 2,2	6,75 ± 2,3	0.11	ns
Wish more pain treatment (P8) %	17,5	33,3	40		**A-C <0.05**
SECONDARY ENDPOINTS	**A**	**B**	**C**		
Drowsiness (P6b)	2,08 ± 2,8	1,42 ± 2,1	2,4 ± 2,8	0.52	ns
Itching (P6c)	0,52 ± 1,2	1,64 ± 2,7	0,45 ± 1,2	**0.0017**	**A-B <0.01** **B-C<0.01**
Nausea (P6a)	1,36 ± 2,2	1,14 ± 2,1	1,35 ± 3,1	0.32	ns
Dizziness (P6d)	0,76 ± 1,7	1,6 ± 2,5	0,85 ± 1,8	0.06	ns
Pain wake up? (P16 v1) %	27,6	45,2	61,7		**A-C <0.005**
TERTIARY ENDPOINTS	**A**	**B**	**C**		
Information about treatment options (P10 v1) %	70,3	41,2	5		**A-B <0.005** **A-C <0.0001** **B-C <0.0005**
Allowed participation on treatment option (P10)	3,68 ± 3,6	3,59 ± 3,5	0,62 ± 1,8	**0.001**	**A-C <0.001** **B-C <0.001**
Use of non pharmacological treatment (P12) %	39	34	22		ns

Table 32. Demographics, primary, secondary and two of the tertiary endpoints in patients undergoing orthopaedic surgery (involving hip or lower limb) and divided per Hospital. Hospitals are also indicated with letters A to C for the multiple comparisons through the Dunn's and Chi-square with Yates correction tests. The p values for multiple comparisons are shown only when significantly different.

In order to understand if the differences seen among the hospitals are attributable to the intraoperative technique, we further divided the population into 3 groups: 1) Regional anaesthesia with a central nerve block (C-B); 2) regional anaesthesia with a combination of a central and a peripheral nerve block (CP-B); 3) General anaesthesia with use of remifentanil (GA-R). We intentionally excluded the other patients undergoing general anaesthesia and those cases in which a general anaesthesia technique was integrated by a nerve block. No patients undergoing anaesthesia with remifentanil received a central or peripheral nerve block. Table 33 shows the differences among the 3 groups.

We further investigated the 3 above mentioned groups by following the use of NSAIDs and/or Opioids and/or regional analgesia with local anaesthetic during the postoperative period spent in the RRA and in the Ward. Table 34 shows the number of patients receiving each particular drug and the various combinations of treatment. Data were not available for 7 patients. The group CP-B showed a significantly higher use of tramadol and a trend towards a reduced use of diclofenac (0.06) when compared with the CN. The comparison of the same group (CP-B) with the GA-R group showed a significantly higher use of paracetamol and tramadol, and a lower use of ketorolac and morphine. The C-B group had a significantly lower use of ketorolac and morphine, and trends towards a larger use of paracetamol (0.06) and less use of tramadol (0.09) when compared to the GA-R group. The GA-R group received morphine and ketorolac more frequently, and paracetamol and diclofenac less frequently when compared to the C-B and CP-B groups.

DEMOGRAPHICS	Central nerve block only (C-B) (N=81) A	Central and peripheral nerve block (CP-B) (N=33) B	General anaesthesia with Remifentanil (GA-R) (N=22) C	P value	Dunn's or Chi-square test (p value)
Male sex %	44,9	56	52,4		ns
PRIMARY ENDPOINTS	**A**	**B**	**C**		
Worst Pain (P1)	5,31 ± 2,9	5,15 ± 2,5	6,13 ± 2,7	0.36	ns
Time spent in Severe Pain (P3) %	33,4 ± 26	26,1 ± 19	36,4 ± 23	0.27	ns
Relief received by treatment (P7) %	63 ± 26	69,7 ± 21	65,2 ± 24	0.43	ns
Satisfaction about pain management (P11)	7,12 ± 2,3	8,09 ± 1,5	7,18 ± 1,9	0.09	ns
Wish more pain treatment (P8) %	35	6,1	36,4		**A-B <0.005 B-C <0.05**
SECONDARY ENDPOINTS	**A**	**B**	**C**		
Drowsiness (P6b)	1,76 ± 2,5	1,15 ± 1,8	3,14 ± 3,4	0.039	**B-C <0.05**
Itching (P6c)	0,84 ± 2	0,67 ± 1,3	0,76 ± 1,5	0.75	ns
Nausea (P6a)	1,39 ± 2,6	0,88 ± 1,8	1 ± 1,7	0.56	ns
Dizziness (P6d)	0,99 ± 1,9	0,73 ± 1,66	1 ± 2,3	0.81	ns
Pain wake up? (P16 v1) %	43,7	34,4	42,1		ns

Table 33. Demographics, primary, secondary and two of the tertiary endpoints in patients undergoing orthopaedic surgery (involving hip or lower limb) and divided according to the intraoperative technique of anaesthesia: 1) regional anaesthesia with a central nerve block (C-B); 2) regional anaesthesia with a combination of central and peripheral nerve block (CP-B); 3) general anaesthesia with use of remifentanil (GA-R). Groups are also indicated with letters A to C for the multiple comparisons through the Dunn's and Chi-square (with Yates correction) tests. The p values for multiple comparisons are shown only when significantly different.

POSTOPERATIVE DRUG ADMINISTRATION	Central Nerve block only (C-B) (N=81) A	Central and peripheral nerve block (CP-B) (N=33) B	General anaesthesia with Remifentanil (GA-R) (N=22) C	Chi square test (p)
Morphine (N=40)	17 (21%)	7 (21%)	16 (72%)	**A-C <0.001** **B-C <0.001**
Tramadol (N=36)	19 (23%)	16 (48%)	1 (4%)	**A-B <0.05** A-C =0.09 **B-C <0.005**
Paracetamol (N=62)	39 (48%)	18 (55%)	5 (23%)	A-C =0.06 **B-C <0.05**
Ketorolac (N=62)	31 (38%)	14 (42%)	17 (77%)	**A-C <0.005** **B-C <0.05**
Diclofenac (N=16)	15 (19%)	1 (3%)	0	A-B =0.06 A-C = 0.07
Regional analgesia (N=4)	2 (2%)	2 (6%)	0	ns

Table 34. Postoperative drug administration for pain relief in the three subgroups of patients undergoing orthopaedic surgery (involving hip or lower limb) according to the intraoperative technique used: 1) regional anaesthesia with a central nerve block (C-B); 2) regional anaesthesia with a combination of central and peripheral nerve block (CP-B); 3) general anaesthesia with use of remifentanil (GA-R). Groups are also indicated with letters A to C for the multiple comparisons through the Chi-square (with Yates correction) test. The p values for multiple comparisons are shown only when significantly different or when the trend is towards a significant difference.

Another analysis was done in the group treated intraoperatively with central nerve block only. We divided this subgroup of patients according to the injection/infusion of local anaesthetic ± additive drugs to strengthen the central block itself. Forty-three patients receiving local anaesthetic only (Bupivacaine n=5; Levobupivacaine n=16; Ropivacaine n=22) were compared to 38 patients receiving an additive drugs when performing the central nerve block (Clonidine n= 6; Fentanyl n= 24; Morphine n=8).

The comparison of these two groups has shown that the group receiving a local anaesthetic only was significantly younger (p=0.009). This group showed a trend towards higher worst pain (p=0.11), while the other primary and the secondary endpoints were not different to those receiving an additive drug for the central nerve block. By excluding from the second group those 6 patients receiving clonidine, the comparison shows no difference at all for the primary and secondary endpoints.

In the overall population undergoing hip or lower limb orthopaedic surgery, the wound was infiltrated in only 7 patients, thus no analysis was performed.

3.5 Urology

We collected a total 169 patients in three Hospitals. This number is unfortunately too low to identify a viable subgroup. Any approach to the data analysis would have been pointless.

4. DISCUSSION

4.1 Evaluation of the scores of the overall Catania population

A general evaluation of the scores is probably of limited importance as the context (patient, surgery, anaesthesia, and hospital) is highly variable. In this framework, even 2441 patients filling a questionnaire are probably not enough. We failed to reach the target number of 3000-5000 intervention within two years. However, we estimate a loss of roughly 1000 patients' data already collected, due to the change of version of the questionnaire (and the web-based mask consequently) promoted by the Pain Out Board on January 2011. This would have allowed us to reach the prefixed target number but, even in that case, the interpretation of the overall data would have had several limitations. For this reason we will focus our discussion mainly on findings of subgroup analysis. Nevertheless, a look at the overall results still allows some general description of pain treatment in Catania's territory.

We believe that the results of primary endpoints in the overall population show that there are large margins for improvement for postoperative pain treatment in our territory. Of the primary endpoints, the level of worst pain (5/10) does not seem to be very high and this is likely to reflect a good initial approach to the postoperative pain by the anaesthetist and generally the operating theatre team. Even if we did not analyse the timing of questionnaire collection as it would have been practically unfeasible, we are sure that most of the questionnaire were filled in on the day after, at some point between late morning and late afternoon, so that most of the patients would have already had their operation performed at least 16 hours before. In this context, a long time spent in severe pain (almost 30%) and suboptimal pain relief received by treatment (63%), together with almost 20% of patients wishing for more PP treatment indicate huge space for improvement in the postoperative treatment in the ward. This is also somewhat confirmed by the findings of the secondary endpoints: we saw fairly low scores of the postoperative side effects (drowsiness, itching, nausea, dizziness) while more than a quarter of the patients were woken up by pain. Furthermore, as tertiary endpoint we saw a decent interference of pain with the in-bed (3,45/10) and out-of-bed (3,78/10) activities, and the importance of early mobilization of patients after surgery is a well-known target to meet for the postoperative period. From these simple results we can speculate that postoperative pain is still underestimated and not properly treated in our area, possibly affecting patient's experience and outcome. Moreover, less than half of the patients stated they were informed of the possible treatment options and allowance to participate in the decisional process was as low as 3,31/10. The above interpretation of our results contrasts with the fairly good level of satisfaction regarding pain treatment (7,6/10) which seems to be sufficiently express a moderate/good degree of gratification. However, we believe that even if the

question was focused on PP treatment, patient's answer regarding this matter may have been affected by other variables not strictly dependent on pain and the role of satisfaction as a primary endpoint should be reconsidered in view of these findings. Moreover, patients may expect pain as results of surgery and can express some level of satisfaction even in presence of suboptimal scores of the other primary endpoints. A meeting with the Pain Out Board has been planned in order to discern if our results coincide or not with the findings from other centres involved in the study.

4.2 Pharmacological considerations on the overall data

We believe that the most important pharmacological finding rises from the overview of the drugs used for PP relief in the overall data, which reasonably describe the general approaches in our territory. As collateral pharmacological findings rising from the overall data analysis, we also point out that patient controlled analgesia has never been used in our territory and that the surgical wound infiltration (which theoretically applies to most of the interventions) is not a diffused practice, being recorded for only 4.3% of patients (n=116/2706).

4.2.1 Overall pharmacological approach to postoperative pain

Excluding those few patients treated with techniques of regional analgesia, we saw a practically exclusive use of morphine and tramadol as opioids, while NSAIDs administration seems to be limited to ketorolac, paracetamol and to a less extent to diclofenac. Both opioids and NSAIDs are consolidated drugs for postoperative analgesia. If the choice between morphine and tramadol depends largely on the level of postoperative pain (being tramadol not as strong as morphine) and a more in-deep discussion would not be worth, some consideration regarding the use of NSAIDs could be useful.

In the last few decades, the concept of multimodal analgesia (the use of different analgesic and techniques to relieve pain), has developed and NSAIDs play a major role. Surgery causes both pain and inflammation. On the opposite of opioids, NSAIDs combine the anti-inflammatory effect to the analgesic activity, also reducing opioid requirements and therefore minimizing their side effects [29-30]. On the other side, both oral and parenteral NSAIDs are also associated with safety concerns in the perioperative setting, being specifically associated with risk of renal failure, gastritis and haemostasis disorders [31].

Unfortunately a limited number of NSAIDs exists in parenteral formulations, that are far more likely used within the first postoperative day, which is the target of this observational study. Ketorolac, diclofenac and paracetamol exists in parenteral formulations and are available at all the centres involved in the study. Among NSAIDs, ketorolac has been the drug most frequently prescribed. Ketorolac was recorded almost 3 times (ratio 1:2,9) more frequently than diclofenac. However, the ratio paracetamol/ketorolac was just 1:1,13. This spread use of ketorolac compared to diclofenac, deserves we mount some awareness about the possible issues related with ketorolac administration.

Until recently ketorolac has been the only parenteral NSAID available in the United States, while on the other side ketorolac supply has ceased in Germany in 1993, and the license to market has been suspended in France [(32)]; other European countries had various degrees of restrictions [(33)]. Recommendations on the use of ketorolac were changed post-marketing in order to emphasize contraindications and the U.S. Food and Drug Administration mandated a cautionary "black box" warning in the package labelling of ketorolac [(34)]. After introduction into general clinical use a decade ago, ketorolac has produced a higher incidence of adverse events than anticipated (based on pre-marketing studies) and than the rate associated with other NSAIDs [(35)]. Phase III clinical (premarketing) trials frequently do not hold sufficient power to reliably detect important adverse drug events [(36)].

Since 1992 the federal Agency for Health Care and Policy Research Acute Pain Guideline recommended explicitly the systemic administration of NSAIDs for postoperative pain relief [(37)]. The analgesic and anti-inflammatory efficacy of ketorolac is a valuable tool in the management of postoperative pain.

The use of NSAIDs provides an opioid dose-sparing effect that should lessen the risk of opioid-associated adverse events. A systematic review of ketorolac efficacy and safety suggests that, depending on the type of surgery, ketorolac had an opioid dose-sparing effect of a mean of 36% and that the level of analgesia seems to be better in patients receiving ketorolac in combination with opioids than with either analgesic alone, in particular 1 hour after surgery. However, the same study did not find a concomitant reduction in opioid side effects (e.g., nausea, vomiting), which could be due to the low overall incidence of some of these side effects [(34)]. We saw the same tendency in the population treated with combination of NSAIDs and opioids in open abdominal uterine surgery. The analysis of this population showed that all the primary endpoints were significantly improved or had a trend towards improvement for those patients treated with combination of Opioids and NSAIDs compared with the two groups receiving Opioids or NSAIDs alone. Thus, the lack of differences in side effects found in this subpopulation of our study could be due to inadequate sample size.

In clinical trials, intramuscular ketorolac, 10 to 30 mg, has been shown to be equianalgesic to morphine, 6 to 12 mg, and propacetamol, 2 gr [38-42]. The analgesic efficacy of ketorolac increases as the dose increases. Accordingly, another study found ketorolac 90 mg superior to 6 and 12 mg doses of morphine for overall pain relief, whereas no significant differences were demonstrated between the 10 mg and 30 mg ketorolac doses and the 12 mg morphine dose. However, in another study increasing the IM ketorolac dose above 60 mg did not increase analgesic efficacy, showing that an analgesic ceiling effect exists for ketorolac [43].

Diclofenac is an arylacetic acid NSAID that possesses analgesic, antipyretic, and anti-inflammatory activity. Because it inhibits both COX-1 and COX-2 with similar efficacy [44], it is considered a non-selective COX inhibitor. Diclofenac has been shown to be safe and effective in the treatment of postoperative pain in several randomized controlled trials [45-52]. In Europe and in Italy (including all the centres involved in our study), an injectable formulation (Voltarol®, 75mg/3mL) is available for both IV and IM administration. The components of Voltarol® formulation requires an IV infusion over 30 minutes, while a novel less irritating formulation (Dyloject®, currently on the market in some European countries but not in Italy) is well tolerated as an IV bolus, thus expediting the onset of analgesia and reducing the risk of thrombophlebitis [53].

In term of safety concerns all NSAIDs do not directly affect blood clotting but all inhibit thromboxane A_2 and prostacyclin, both important for clot formation. A significant impact on the coagulation system by ketorolac has been pluri-confirmed. Animal' models and studies on healthy volunteer have shown a significant reduction in platelets aggregation and prolongation of bleeding time [54-56] with no observable dose response [57]. Because the half-life of ketorolac is 6 hours, platelet function returns to normal 24 to 30 hours (five half-lives) after a single dose [58]. Both preoperative use and intraoperative use of ketorolac increases the risk of postoperative bleeding after tonsillectomy [59] and many other anecdotal reports attributing postoperative haemorrhages to ketorolac administration have been published [60-62]. Although in most of the patients the effects of ketorolac on bleeding may be inconsistent, this effect can become more important if patients have other risk factors for bleeding or where even a small perioperative bleeding may largely compromise the efficacy of surgery and expose the patients to unacceptable risks (spine surgery). Diclofenac has a shorter half-life than ketorolac and a recent 4-treatment crossover study in healthy male volunteers confirmed that diclofenac i.v. bolus affects platelet function to a lesser extent than the predominantly COX-1 inhibiting NSAIDs, such as ketorolac and acetylsalicylic acid [63]. The more "balanced" COX-1/COX-2 inhibition by diclofenac is likely to determine less interference on coagulation and can be attractive in the postoperative setting. Anyway, all the animal and healthy volunteer studies require more confirmation in the postoperative clinical settings where surgical stress may impact on platelet

function, and where larger populations comprising different genders, diverse races, and patients with co-morbidities are exposed.

Moreover, ketorolac has been investigated regarding its gastro-toxicity and a matching study of outpatients with gastroduodenal lesions showed that among NSAIDs, ketorolac is the only with a distinctly elevated risk of gastroduodenal lesions (odds ratio 4.2) [(64)]. In another large study, ketorolac was found to be five times more gastrotoxic than all other NSAIDs (relative risk 5.5). Ketorolac risk remained high even at lower doses (i.e., 20 mg or less) [(65)] and in 1997 the sole American manufacturer of ketorolac at that time, Roche Laboratories®, made alterations to the package labelling of Toradol® to reflect more stringent guidelines for doses, duration, and age-based dosing [(66)].

Another safety issue with NSAIDs concerns the risk to develop acute renal failure, which is more prominently a fear for elderly patients with congestive heart failure, hepatic cirrhosis, hypovolaemia, or an underlying renal disorder [(67)]. A recent large retrospective study found that adjusted odds ratio for acute kidney injury was 1.11 for diclofenac and 2.07 for ketorolac [(68)]. Acute renal failure has been reported after ketorolac, but toxicity usually reverses after discontinuation and seems a dose-related phenomenon with a relative risk of 2.08 when ketorolac is administered for > 5 days [(69-71)], and a Cochrane collaboration review concluded ketorolac administered for 5 days or less did not increase the rate of renal failure. There was no significant difference in serum creatinine in the early postoperative period between patients receiving ketorolac and diclofenac, and generally the conclusion was that NSAIDs cause a clinically unimportant and transient reduction in renal function in the early postoperative period, but they should not be withheld from adults with normal preoperative renal function because of concerns about postoperative renal impairment [(72)].

In summary, a challenge for the clinician is to select a ketorolac dose that balances the risk of bleeding and gastropathy with analgesic effectiveness or to choose alternative strategies. Due to its potential risks ketorolac administration should be carefully balanced with valid alternatives. Among them diclofenac seems to be a valid substitute that may have potential benefits in term of safety, affecting of a less extent the coagulation system (even at the higher concentration reached by the novel IV bolus formulation - not available in Italy at present).

Other important pharmacological considerations are discussed one by one over the next paragraphs, as rising from the observation from one or more subpopulations of the study.

4.2.2 Patient Controlled Analgesia

Regarding the use of PCA, the evidence is not strong at present. The Australian and New Zealand College of Anaesthetist and the Faculty of Pain Medicine have recently produced the third edition of a document regarding the scientific evidence in acute pain management [73]. This document highlights that, even though the iv opioid PCA provides better analgesia than conventional (i.m. or s.c.) opioid regimens and the patient satisfaction scores higher, the magnitude of the difference in analgesia between conventional and PCA regimen is small (about 8 points on a pain scale of 0 - 100). Furthermore opioid consumption determined by PCA is greater and there are no differences in duration of hospital stay or opioid-related adverse effects other than pruritus, which is increased [74]. However**,** information obtained from published cohort studies, case-controlled studies and audit reports only [75] suggests that i.v. PCA may be more effective than intermittent i.m. opioid analgesia in a 'real life' clinical setting, with decreased incidence of moderate-to severe pain and severe pain.

A question remains in term of organizational structure as settings where there are high nurse/patient ratios and where it might be easier to provide analgesia on-demand and conventional approach to pain relief could be as effective as i.v. PCA. In example, a comparison of PCA versus nurse-administered analgesia following cardiac surgery found no difference in analgesia at 24 hours (a period when nursing attention is likely to be higher) but significantly better pain relief with PCA at 48 hours [76]. Perhaps, the enormous variability in PCA parameters (bolus doses, lockout and maximum allowed cumulative doses) used in many studies complicates the analysis.

The use of PCA also requires consideration of the cost involved. There are no good, consistent data on the cost-effectiveness of PCA compared with conventional opioid analgesic techniques; information that is available often does not include the full scope of costs (i.e. cost of adverse events or failure of an analgesic technique as well as the more obvious costs of pumps, disposables and nursing time). However, in general, PCA comes at a higher cost because of the equipment, consumables and drugs required; nursing time needed is much less [77-80]. With the level of evidence at present and the financial crisis involving our territory, the discussion regarding the implementation of a PCA programme does not seem to be a priority.

4.2.3 Surgical wound infiltration

The above mentioned third edition of the document on acute pain management by the Australian and New Zealand College of Anaesthetist [73] deals also with the scientific evidence of wound infiltration including wound catheters. A meta-analysis reviewed outcomes following postoperative analgesia

using continuous local anaesthetic wound infusions. Analyses were performed for all surgical groups combined and for single subgroups (cardiothoracic, general, gynaecology-urology and orthopaedics). While there were some minor variations between the subgroups, the overall results showed that this technique led to reductions in pain scores (at rest and with activity), opioid consumption, PONV and length of hospital stay; patient satisfaction was higher and there was no difference in the incidence of wound infections [81].

Continuous infusion of ropivacaine into the wound after appendicectomy was superior to a saline infusion [82] as was a continuous wound infusion of bupivacaine after open nephrectomy [83]. Infusion of ropivacaine into the site of iliac crest bone graft harvest resulted in better pain relief compared with i.v. PCA alone and significantly less pain during movement at 3 months [84]. Early postoperative abdominal pain was improved after laparoscopic cholecystectomy by the use of intraperitoneal local anaesthetic; the effect was better when given at the start of the operation compared with instillation at the end of surgery [85]. Preperitoneal infusion of ropivacaine after colorectal surgery resulted in improved pain relief, opioid-sparing and earlier recovery of bowel function [86].

Further guidelines have been endorsed by the European Society of Regional Anaesthesia and Pain Therapy in the PROcedure SPEcific postoperative pain management – "PROSPECT" http://www.postoppain.org/frameset.htm - a working group aiming to identify the evidence in the literature for each single surgical intervention.

Regarding the wound infiltration with local anaesthetic vs placebo, administered intra-operatively in patients undergoing abdominal hysterectomy, eight studies examined the effect of different infiltration regimens (by local injection combined or not with epinephrine or NSAIDs) compared with placebo or no infiltration. Six of eight studies showed no significant benefit of wound infiltration [87-92] while the remaining two showed a significant benefit for reducing supplementary analgesic consumption at 0–4 h [93] and at 1, 2 and 4 h [94].

In patients undergoing laparoscopic cholecystectomy, intraoperative wound infiltration with local anaesthetic was superior to pre-incisional administration, which in turn was superior to placebo for reducing pain scores and proportion of patients requiring postoperative analgesics [95]. In the same setting, intra-operative wound infiltration plus intraperitoneal administration of bupivacaine reduced postoperative overall pain and incisional pain for the first 2-3 hours, as well as 3-hours morphine consumption and nausea [96].

Most of these results seem to be of short duration and a study in patients undergoing breast non-cosmetic surgery reported that pain scores at rest on admission to and during recovery room area stay

were significantly lower with preoperative bupivacaine wound infiltration compared with placebo. However this advantage was lost during the step-down stay and generally at discharge or at 24 h after surgery [97].

We saw a very low incidence of wound infiltration in our Area, in all cases performed as single shot by the surgeon. As discussed, the level of evidence is not strong enough to issue a recommendation in our territory. Perhaps, many studies looked at continuous wound infiltration which seems a practice not used in our territory. Speculating that the evidence is not strong because advantages in pain management offered by the infiltration of wound could be small (and in case of single injection of limited duration), to increase the likelihood of finding a beneficial impact would need of a great number of patients. Pain Out registry could be the solution for this dilemma, but in our area the contribution seems to be low and a discussion with our Hospitals seems reasonable.

Nevertheless, in the only subgroup of Catania's population allowing analysis, female patients undergoing caesarean section and receiving wound infiltration showed worse results for 2 primary outcomes (relief received by treatment and time spent in severe pain). In consideration of the short-lasting effects of wound infiltration in single shot that is more likely to affect just the initial phase of PP, we believe that this results is casual and most likely driven by other factors. Moreover, the small number of patients receiving wound infiltration does not allow definitive conclusions.

4.3 Limitations

Even if not conventional, study and analysis limitations should be discussed before the discussion of the findings of the subgroup analyses as they apply to most of them.

- The Pain Out Project is designed for the collection of a huge number of cases in order to minimize the possible bias and to increase the number of data for each type of intervention and patient's characteristics. Our data analysis on small populations is often under-powered to detect significant differences;

- This analysis did not voluntarily take into account the exact timing from surgery to data collection, so that the pharmacological analysis has been restricted to the qualitative evaluation rather than to the quantitative analysis of the amount of drug given. Anyway, the qualitative analysis still allows a good description of the approach to postoperative pain relief in our territory;

- The questionnaire has been validated for clinical purpose but its interpretation may still suffer of cultural background. We saw 180 cases with a reported worst pain lower than the least pain score.

Even if we obviate to this issue by inverting those values, this shows the potential for patient's misunderstanding and thus for some loss of precision by the questionnaire. Moreover, even if the aim of the questionnaire is clearly focused on postoperative pain treatment, some answers are likely to be affected by many other factors that are not strictly related to the pain issue (i.e. the nurse's and doctor's attitude, underlying disease and psychological status, etc).

- We intentionally did not exclude those with pre-existing chronic pain and we did not consider the degree of patient's co-morbidities. This approach was chosen in order to avoid further cuts of data which helps for the subgroup analysis and generally to give us a more *real-life* perspective.

- Even if a small imprecision in the calculation of the age is unlikely to significantly affect the treatment of postoperative pain, the year of birth has to be interpreted carefully in view of the date of collection of the data, as the study is moving forward along the years.

4.4 Subgroup analysis

4.4.1 Remifentanil and worse outcome

One of the most interesting findings in our study has been a correlation between the use of intraoperative remifentanil and worse scores in some primary outcomes. Interestingly, this result was found in two different subgroups - thyroidectomies and open abdominal uterine surgery.

In both subgroups we saw a higher reported worst postoperative pain for those patients anaesthetized with remifentanil. In the subgroup undergoing thyroidectomies this results was coupled with lower satisfaction regarding pain management, while in the open uterine surgery subgroup receiving remifentanil anaesthesia showed a trend towards more time spent in severe pain.

Those findings in the primary outcomes go along with worse scores also in some secondary outcomes. In both surgical sub-populations treated with remifentanil we observed higher incidence of dizziness, nausea and pain-related waking up. Furthermore, those receiving remifentanil during thyroidectomy showed higher level of itching, while the uterine surgery subgroup receiving remifentanil showed more drowsiness.

Of course the findings in the outcomes should be interpreted in view of the intraoperative and postoperative drugs used to prevent postoperative pain. Unfortunately, as already mentioned, the analysis of the intraoperative period is somewhat difficult as some drugs in the intraoperative period could have been given at the induction of anaesthesia rather than at the end of surgery. This is the case

of fentanyl and morphine. As specified in the methods, we reasonably assumed that fentanyl has been used prevalently for the induction of anaesthesia (and for the maintenance in those patients not receiving remifentanil) rather than as a tool to control postoperative pain. On the other side, morphine and tramadol are far more likely to be used before the emergence from anaesthesia in order to manage postoperative pain rather than during the induction and/or maintenance of anaesthesia. For this reason, the interpretation of our results is made on the speculation that only morphine and tramadol were used as opioids for the PP management as well as for the administration of NSAIDs. The quantitative analysis of the dosages has not been performed and only the qualitative assessment – given *vs* not given – has been accomplished. We found conflicting results regarding the use of intraoperative drugs for pain relief. Patients undergoing thyroidectomy with use of intraoperative remifentanil had more frequent use of Opioids and NSAIDs (tramadol and ketorolac). Conversely, the group undergoing uterine surgery with remifentanil infusion received less frequently intraoperative tramadol and generally showed a trend towards less use of intraoperative opioids.

Surprisingly, the analysis for the postoperative period showed that patients exposed to remifentanil for thyroidectomy received less frequently opioid medications, and those undergoing open uterine surgery and anaesthetized with remifentanil showed a trend towards less frequently administered NSAIDs.

These results together may indicate that a suboptimal treatment in those patients receiving remifentanil may have had place and that some degree of attention should rise locally towards those patients anaesthetised with remifentanil. In order to understand if this is a local problem or a more diffuse issue, our intention is to discuss these findings with the PAIN OUT Board eventually looking at this issue for a larger group of patients.

Some pharmacological consideration may help to better understand the rationale of the worse results of the remifentanil group and the reason why we should raise the attention of healthcare providers regarding the remifentanil use.

Remifentanil has unique pharmacological properties and is the opioid of clinical use with the shortest half-life. Remifentanil clearance is not affected by the duration of its infusion ("context-insensitive") so that its withdrawal leads to a quick disappearance of analgesic effect. Regardless the good level of intraoperative stability provided by remifentanil, the postoperative period may be characterized by a more challenging pain control. In fact, remifentanil has been investigated for causing acute opioid tolerance and hyperalgesia, causing worse pain scores and higher request of analgesic rescue doses. The mechanisms mediating opioid-induced hyperalgesia would include activation of NMDA receptors, protein kinase C and facilitatory supraspinal loops [98-99].

The debate on hyperalgesia and opioid tolerance by remifentanil is ongoing and there are conflicting studies. Guignard et al. [100] showed a correlation between larger doses of remifentanil and greater postoperative pain scores in patients undergoing major abdominal surgery, all together with increased morphine consumption. The most likely explanation given by the authors pointed towards the development of acute opioid tolerance, which can explain as well the larger doses of morphine for those treated with higher doses of remifentanil. More recent studies reinforce this hypothesis and are trying to define strategies to limit hyperalgesia. An interesting study by Joly et al. [101] found that relatively large dose of intraoperative remifentanil triggers postoperative secondary hyperalgesia that can be attenuated by administration of ketamine. Patients undergoing major abdominal surgery were randomly assigned to low dose remifentanil, high dose remifentanil or high dose remifentanil in association with ketamine. At 24 and 48 postoperative hours pain and postoperative morphine consumption were significantly greater in the high-dose remifentanil group than in the other two groups. These findings reinforce the hypothesis that remifentanil dose is important in determining postoperative hyperalgesia and that the blockade of NMDA-receptors can be used prevent hyperalgesia. Not only ketamine, but magnesium sulphate has been investigated for the prevention of postoperative remifentanil-induced hyperalgesia [102]. Unfortunately in our study we cannot easily and precisely determine the dose of remifentanil. Ketamine is not available in our territory and the dataset does not include the administration of magnesium. A discussion with the centres involved in this study has shown that no one has ever implemented a protocol for preventing hyperalgesia through administration of magnesium sulphate and that it is generally unlikely the administration of magnesium unless patient develops cardiac arrhythmias. Nonetheless, a study by Cortinez et al. [103] did not find a correlation between remifentanil and postoperative hyperalgesia in patients undergoing elective open gynaecological surgery. However, in this study the doses of remifentanil used were smaller than the ones used by Guignard et al. [100], again rising concerns regarding the intraoperative use of remifentanil. Anyway, the use intraoperative remifentanil should be still titrated to avoid high doses, which have larger chances to induce hyperalgesia and acute opioid tolerance, at least until validated strategies will be available to offset this issue.

In conclusion, despite the ongoing debate on remifentanil-induced hyperalgesia and its optimal intraoperative dose, regardless the investigations on possible strategies to prevent hyperalgesia and until evidence based approaches will be developed, the anaesthetist and all the personnel dealing with the surgical patients should be aware of the impact that intraoperative anaesthesia with remifentanil can have on the management of postoperative pain. It would be optimal to spread the message to all the healthcare providers and to highlight the need for a carefully planned postoperative strategy for pain relief for those patients undergoing anaesthesia with remifentanil.

4.4.2 Differences Among Hospitals

4.4.2a Public vs Private Italian Healthcare System (IHS)

Among the four typology of surgery involved in the study and collecting data in Catania, general surgery was the only one involving centres of the private IHS, thus potentially allowing a comparison with the public IHS. So far, the sample size allowed us to trace a comparison between the two systems only for patients undergoing thyroidectomy. In this setting we found interesting results showing a much improved outcome of the patients treated in the private Hospitals with all the primary endpoints significantly improved.

The differences in endpoints results between the two IHS are far more pronounced rather than the ones seen in the comparison regarding the use of intraoperative remifentanil. Moreover, remifentanil does not seems to largely contribute to the differences between public and private HIS as it has been used prevalently in Vittorio Emanuele Hospital (public) and Humanitas Institute (private), with only one case with remifentanil use recorded at Oncological Mediterranean Institute. On the other side most of the cases without intraoperative administration of remifentanil were conducted at Garibaldi Nesima (public) and Oncological Mediterranean Institute (private), with only other three cases contribution by Vittorio Emanuele Hospital (n=2) and Humanitas Institute (n=1).

It is difficult for us to explain the reasons for these differences and thus to find the way to improve the system itself. We are considering an in-deep discussion with the Directors of the Anaesthesia and Postoperative pain service of the 4 Trust involved. A sensible approach could be to blind them from to decrease the risk of future interference on the ongoing data collection. We would like to highlight the strength and the weakness of each institution.

Regarding the other endpoints, we saw higher dizziness (2,9/10) and drowsiness (3,4/10) in the population treated by the private IHS. However, the level of these side effects does not seem to achieve a point that should trigger further discussion. Itching was significantly higher in the population of the public HIS; however its levels are so low in both populations that it should not be seen as a sentinel of concern.

The use of non-pharmacological methods was more spread in the private IHS. A further analysis showed those using non-pharmacological approaches for pain relief as suffering higher level of worst pain and time spent in sever pain plus a trend towards lower relief received by treatment. Moreover these patients were more frequently woken up by pain and experienced more drowsiness. Most likely, those patients using non-pharmacological tools for pain relief have already been treated with pharmacological therapy experiencing suboptimal treatment.

Finally and very interestingly, more information about options for pain relief have been given in the hospitals of the public IHS together with a trend of higher allowed participation in the plan for management of postoperative pain. However, this does not seem to improve the outcome of the patients.

4.4.2b Hospitals of the Public IHS

There have been many differences among different Hospitals of our territory as highlighted by the analysis of subpopulations. The discussion of the reasons for this disparity is not easy and requires meetings and in-loco investigations. The presence and implementation of protocols for postoperative pain treatment could be just one of the factors contributing to different outcomes and it will be analysed in future meetings.

4.4.3 Opioid adjunct for spinal anaesthesia in Caesarean Section

We compared the outcomes between the two more representative groups of CS in which bupivacaine have been used in combination with morphine or fentanyl. The results of this comparison did not show any difference in the outcomes between the two groups. Our study was not set to evaluate the length to the first analgesic requirement that is a primary endpoint of studies trying to address the optimal therapeutic option. Furthermore, the dose administered and other side effects typically investigated by trials (i.e. nausea, itching, hypotension and vasopressors requirements) were not part of our database. We focused on patient's perspectives and, not surprisingly, a well executed central nerve block can provide good intra- and postoperative comfort, regardless the drugs used. However, what seems to be confirmed by a review of the recent studies and meta-analyses is that it would be preferable to add an opioid to the local anaesthetic for spinal anaesthesia in female undergoing CS. Indeed, intrathecal administration of local anaesthetics alone provides anaesthesia of shorter duration and is less effective in controlling the nausea–vomiting induced by surgical uterine manipulations than the combined intrathecal administration of local anaesthetic and opioid. Moreover patients request analgesics earlier during the postoperative period when treated with intrathecal local anaesthetic alone [(104-105)]. A recent meta-analysis [(106)] of three different drug regimens of bupivacaine in spinal anaesthesia for CS found that the combination of low-dose bupivacaine with opioids not only reduced intra-operative hypotension but also provided reliable analgesia suggesting that the combination regimen should be considered as first choice, in absence of contraindications. Moreover, even if conducted in non-CS surgery, another recent meta-analysis [(107)]. including 65 randomized trials found that morphine

and fentanyl added to bupivacaine were the most frequently combination tested. The duration of postoperative analgesia was prolonged with both morphine and fentanyl when compared to the local anaesthetic alone. A study of patients undergoing CS [108] showed that adding intrathecal morphine to levobupivacaine prolongs the duration of spinal analgesia and provided rapid onset of action and longer time to first analgesic request. In our findings only one patient received a spinal anaesthesia without the use of an opioid adjunct. This result shows that medical practice for patients undergoing CS follows the current clinical evidence. However, the population of study is representative of only one Hospital (S. Bambino) so that a generalization spread to the entire territory of Catania would be hazardous.

The type of local anaesthetic used and its concentration may also play an important role. An interesting study [109] by Saracoglu et al. showed that intrathecal morphine provides longer duration of postoperative analgesia when it is combined with plain bupivacaine instead of heavy bupivacaine. Unfortunately, our database does not support the recognition of different concentrations of local anaesthetic used so that we cannot address this issue.

We found accounts for only two intraoperative opioids for regional anaesthesia - morphine and fentanyl, being the first one used almost three times more than fentanyl. An interesting randomized double-blind controlled trial examined the effects of fentanyl and morphine, alone and in combination, as adjuncts to intrathecal bupivacaine in CS [110]. The quality of postoperative analgesia with morphine, when used alone, was superior to that with fentanyl, while the combination of opioids offers no advantages over morphine alone. In our study we do not have evidence of any spinal anaesthesia performed with the combination of two opioids and the current literature does not seem to support this approach. Another randomized double-blind study [111] analyzed the effect of intrathecal fentanyl or morphine combined with levobupivacaine for patients undergoing CS. Patients treated with fentanyl earlier required additional analgesic treatment and in larger amount if compared with morphine. In our population we found a larger use of tramadol and a trend towards more use of paracetamol in those patients receiving fentanyl as adjunct to the local anaesthetic, while the use of diclofenac was significantly higher for those patients receiving intrathecal morphine. A trend toward higher use of drugs combination for pain relief was seen for the patients with use of intrathecal bupivacaine and fentanyl. A larger sample would have maybe allowed detecting some differences in the use of postoperative drugs. The same study by Acar [111] et al found also higher satisfaction among the patients treated with morphine as adjunct for spinal anaesthesia in CS. In our study we found a prevalent use of morphine as intrathecal adjunct to the local anaesthetic. However, we were not able to show any difference in patient's satisfaction. It is not possible to deny a possible influence of the

small sample size and the different doses used. Larger studies may be required to address if morphine can improve patient's satisfaction.

From these several studies and meta-analysis it is clear the good outcome achieved by the use of opioid in spinal anaesthesia which suggests to use them in combination with local anaesthetics whenever possible. The S. Bambino Hospital met this standard and morphine was the drug prevalently used for this purpose.

In term of side effects, we found that most of the secondary endpoint showed lower scores than the overall Catania's population and the other subpopulations analysed. Nausea is difficult to evaluate as it is common also during the intraoperative period, being related to uterine manipulations and peritoneal closure. The adjunct of an opioid to the intrathecal local anaesthetic has been shown to reduce the incidence of intraoperative nausea [105]. However, nausea has been reported to occur far more frequently in the postoperative period [112]. In our CS population, nausea had lower values than the overall population and does not seem to reach the level of clinical alert. Itching is a relatively minor, but common side effect of central neuraxial opioid administration with an incidence of 50–90% [113]. In our population, the level of itching is not probably high enough to raise the level of clinical alert. Unfortunately the study is not tailored to detect administration of any drugs for itching treatment or symptomatic relief. In contrast to the transient pruritus caused by highly lipid soluble opioids (i.e. fentanyl), morphine usually causes more severe and prolonged pruritus. We did not see differences in the level of itching for those CS-patients receiving intrathecal fentanyl or morphine. Even if itching score was lower in those receiving fentanyl rather than morphine, the result is not statistically significant. We cannot exclude that the small sample size may have negatively influenced the chance to detect a difference among the two regimens.

Finally, this is a single centre analysis. S. Bambino Hospital is a prevalently gynaecological centre with consolidated protocols for the management of the caesarean delivery. Therefore it is not unexpected the finding of a better scores among the primary and most of the secondary outcome when looking at the absolute mean of caesarean sections population and other centres/intervention results. The practice of S. Bambino for CS seems to meet the current state of the art.

4.4.4 Peripheral nerve block in hip and lower limb orthopaedic surgery

In this subpopulation we aimed to show differences among the endpoints according to the intraoperative technique of anaesthesia by comparing the regional approach (with or without the use of a peripheral block) and the general anaesthesia conducted with use remifentanil. Our hypothesis was that the use of techniques of regional anaesthesia over the general anaesthesia would have produced an improvement of patient's outcomes. Unfortunately we failed to show major changes and among the primary endpoints, only a significantly lower wish to receive more pain treatment was found for those treated with regional anaesthesia using a combination of a central and peripheral nerve block compared with the other two populations. However, we saw (non significant) differences between all mean values (both for primary and secondary outcomes) that deserve further analysis with larger sample size. The literature confirms that the use of regional anaesthesia technique should produce benefits. Two meta-analyses have shown that spinal anaesthesia for the treatment of hip fracture/replacement confers better outcome over general anaesthesia [(114)] and other advantages such as earlier mobilization and lower incidence of deep vein thrombosis [(115)].

If the finding of the literature will be associated with better patient's endpoints score in the next analysis, we may then discuss results with our orthopaedic centres and encourage them to look forward to those anaesthetists skilled to perform peripheral nerve block. In this scenario, Hospitals with an Orthopaedic service should be encouraged to promote staff development in this area.

4.4.5 Future targets and analysis

We are targeting to continue the study despite the economic crisis is affecting it by a reduction of the residents of the School of Anaesthesia and Intensive Care in Catania. These preliminary results are also useful in showing which hospital and which surgical setting is more likely to be rewarding in the data collection. Ideally we would like to enlarge the number of data for those interventions amenable of analysis. These results have been shown preliminarily to the Pain Out Board and on the base of our findings we believe is worth to plan some investigations on the overall Pain Out data to confirm or not our hypothesis (i.e. that the use of intraoperative remifentanil may affect negatively the postoperative experience of patients).

As local strategy, we are planning to show these results to our community but maintaining the anonymousness of the centres in order to avoid future interference with the ongoing data collection.

Moreover, we found some differences in the mean values that were not able to reach the statistical significance. This will be further investigated once the sample size will be enlarged, seeking if the absence of statistical significance is at least partially attributable to the small number of cases.

5. CONCLUSIONS

This study describes and analyses over 2400 questionnaire data collected within the observational phase of the PAIN-OUT project. As main results we showed the feasibility of data collection through a model based on the residents of the School of Anaesthesia and Intensive Care of the University of Catania. Moreover, Catania's contribution to the overall worldwide data collection has been outstanding. Pain Out Board is looking forward to hear more about our organization in order to empower other centres in the data collection following our methodology.

From a local perspective, postoperative pain treatment in the territory of Catania seems to have space for improvements, especially in the wards, being sub-optimal the relief received by treatment, the time spent in severe pain and the number of patients claiming for additional postoperative pain treatment. In order to achieve these improvements, a mandatory step is to make caregivers aware of this issue. We are planning a meeting to discuss our results with our community.

Some interesting findings are also found in the subgroup analysis.

In particular:

1. Postoperative pain after thyroidectomy seems to be treated better in the private Healthcare System. We cannot address the reasons for it, but efforts should be made by the community to improve the service offered by the public Healthcare System.

2. There are also consistent differences of patient's outcomes regarding postoperative pain management between all the Hospitals in our territory as shown by the analysis of subpopulations of different specialties. Efforts should be made by the community in order to understand the reasons and to ameliorate the standards by following the model of those Hospitals performing better.

3. The use of remifentanil and the consequent possibility to develop remifentanil-induced hyperalgesia could be reconsidered by the anaesthetist when there is a concern regarding the postoperative pain follow-up by the ward personnel. Efforts should be made to decrease the risk of remifentanil induced hyperalgesia and to improve the treatment of those patients receiving intraoperative remifentanil.

4. On the basis of the results of the S. Bambino Hospital for those patients receiving spinal anaesthesia with the adjunct of a intrathecal opioid, and of the findings in the literature, we would recommend that all the caesarean section should be performed using an opioid. Those patients receiving intrathecal morphine rather than fentanyl could require less frequently a combination of drugs to manage postoperative pain.

We are aware that small sample size and study design may have affected our analysis by hiding some other significant difference. We believe that the differences seen in our subgroup analysis should be investigated in larger samples. We are planning to update our analyses once the sample of data collection in Catania will be larger and also to consider some analysis in the same subgroups (i.e. remifentanil anaesthesia) of the overall data collected so far in Pain Out Project.

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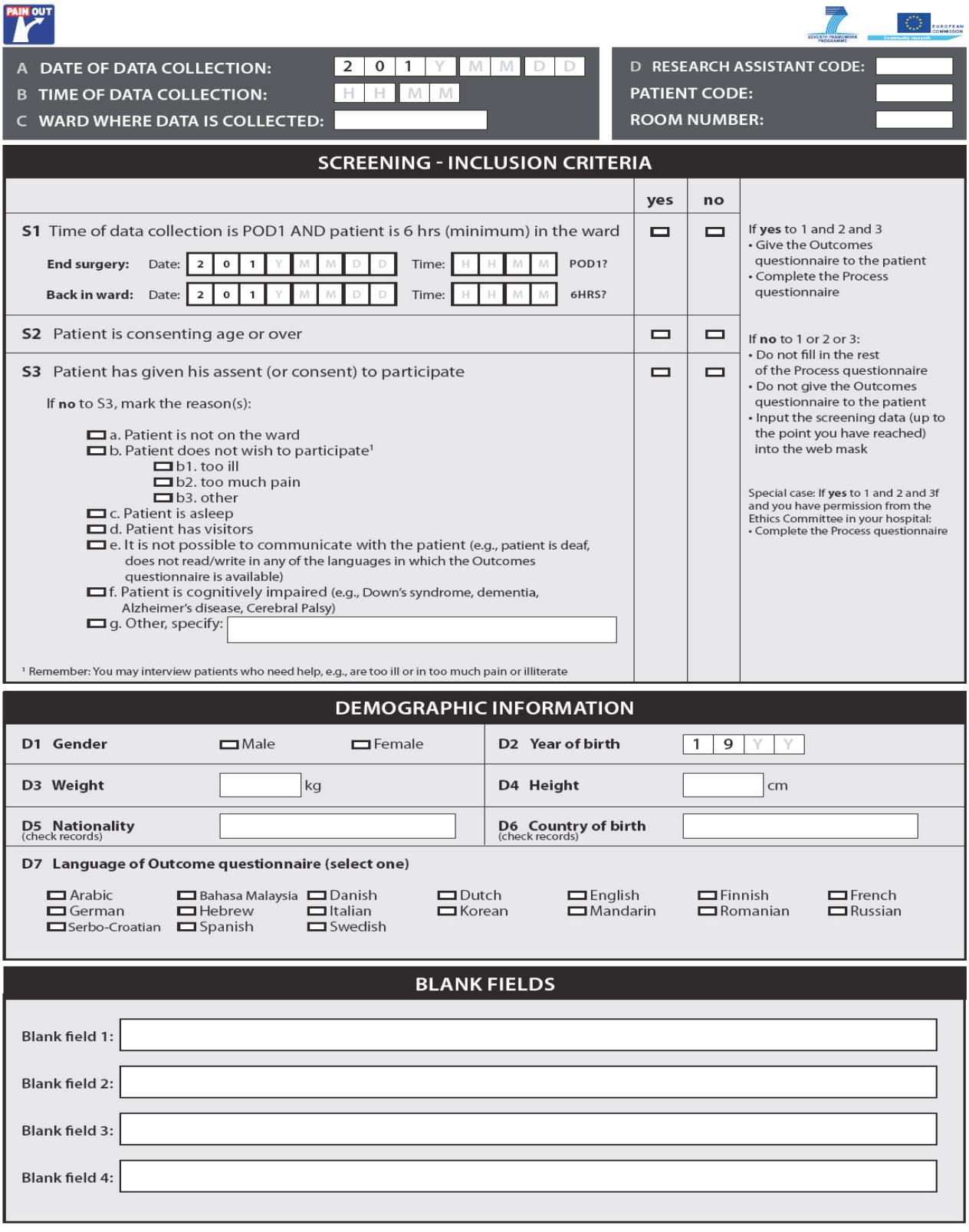
7. APPENDICES

Appendix 1



PAIN OUT

A DATE OF DATA COLLECTION: 2 0 1 Y M M D D
B TIME OF DATA COLLECTION: H H M M
C WARD WHERE DATA IS COLLECTED:

D RESEARCH ASSISTANT CODE:
PATIENT CODE:
ROOM NUMBER:

SCREENING - INCLUSION CRITERIA

	yes	no
S1 Time of data collection is POD1 AND patient is 6 hrs (minimum) in the ward **End surgery:** Date: 2 0 1 Y M M D D Time: H H M M POD1? **Back in ward:** Date: 2 0 1 Y M M D D Time: H H M M 6HRS?	☐	☐
S2 Patient is consenting age or over	☐	☐
S3 Patient has given his assent (or consent) to participate	☐	☐

If **yes** to 1 and 2 and 3
- Give the Outcomes questionnaire to the patient
- Complete the Process questionnaire

If **no** to 1 or 2 or 3:
- Do not fill in the rest of the Process questionnaire
- Do not give the Outcomes questionnaire to the patient
- Input the screening data (up to the point you have reached) into the web mask

Special case: If **yes** to 1 and 2 and 3f and you have permission from the Ethics Committee in your hospital:
- Complete the Process questionnaire

If **no** to S3, mark the reason(s):

- ☐ a. Patient is not on the ward
- ☐ b. Patient does not wish to participate[1]
  - ☐ b1. too ill
  - ☐ b2. too much pain
  - ☐ b3. other
- ☐ c. Patient is asleep
- ☐ d. Patient has visitors
- ☐ e. It is not possible to communicate with the patient (e.g., patient is deaf, does not read/write in any of the languages in which the Outcomes questionnaire is available)
- ☐ f. Patient is cognitively impaired (e.g., Down's syndrome, dementia, Alzheimer's disease, Cerebral Palsy)
- ☐ g. Other, specify:

[1] Remember: You may interview patients who need help, e.g., are too ill or in too much pain or illiterate

DEMOGRAPHIC INFORMATION

D1 Gender	☐ Male ☐ Female	**D2 Year of birth**	1 9 Y Y
D3 Weight	kg	**D4 Height**	cm
D5 Nationality (check records)		**D6 Country of birth** (check records)	

D7 Language of Outcome questionnaire (select one)

☐ Arabic ☐ Bahasa Malaysia ☐ Danish ☐ Dutch ☐ English ☐ Finnish ☐ French
☐ German ☐ Hebrew ☐ Italian ☐ Korean ☐ Mandarin ☐ Romanian ☐ Russian
☐ Serbo-Croatian ☐ Spanish ☐ Swedish

BLANK FIELDS

Blank field 1:
Blank field 2:
Blank field 3:
Blank field 4:

Version2.6 110217

Mark medications *given* to patient; record *cumulative* doses. PATIENT CODE:

MEDICAL HISTORY

H1 Comorbidities

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (check all that apply):

Cancer	☐ **Cancer**
Renal	☐ **Renal** insufficiency or disease **without dialysis** ☐ **Renal** disease **requiring dialysis**
Psychiatric	☐ **Affective disorders** (depression, anxiety, phobia, PTSD, bipolar disorder) ☐ **Schizophrenia** ☐ **Alcohol** use disorder ☐ Current **smoker** ☐ **Substance abuse** of drugs (legal and illegal)
Cardiovascular	☐ **Hypertension** ☐ **Coronary artery** disease or **myocardial infarction** or **cerebral vascular accident**
Hematology	☐ **Sickle cell disease**
GI disease	☐ **Liver Cirrhosis** ☐ History or current upper or lower **GI ulcer** (peptic or duodenal ulcer disease) ☐ **Irritable bowel disease** (Crohn's disease, ulcerative colitis)
Pulmonary disease	☐ **Asthma** ☐ **Sleep apnea** ☐ Chronic Obstructive Pulmonary Disease (**COPD**)
Neurologic	☐ **Fibromyalgia**
Steroid use	☐ Regular administration of **oral or parenteral corticosteroid** medications
Multiple trauma	☐ At least 1 **fracture**(s) / **laceration**(s) / **tissue damage** in addition to the current reason for surgery
Other surgery	☐ Patient has already undergone **another surgery** during current hospitalization
	☐ **Other**, specify:

H2 Existing condition (check medical record)

☐ Pregnancy, Week: ☐ not relevant ☐ not possible to obtain the information

☐ Lactation ☐ not relevant ☐ not possible to obtain the information

H3 Did the patient receive any opioid(s) before the current admission?

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

	Immediate release (PO & other)	Controlled release; (PO & other)
Buprenorphine	☐ mg\day	☐ µg\hr transdermal
Codeine	☐ mg\day	☐ mg\day
Fentanyl	☐ µg\hr transmucosal / intranasal	☐ µg\hr transdermal
Hydrocodone	☐ mg\day	☐ mg\day
Hydromorphone	☐ mg\day	☐ mg\day
Morphine	☐ mg\day	☐ mg\day
Oxycodone	☐ mg\day	☐ mg\day
Oxycodone (with Naloxon)	☐ mg\day	☐ mg\day
Pethidine (Meperidine)	☐ mg\day	☐ mg\day
Tapentadol	☐ mg\day	☐ mg\day
Tilidin (w\wo Naloxon)	☐ mg\day	☐ mg\day
Tramadol	☐ mg\day	☐ mg\day
Other, specify:	☐	☐
Other, specify:	☐	☐

Mark medications *given* to patient; record *cumulative* doses.

PATIENT CODE:

PRE - MEDICATION

M1 Sedatives (pre-medication)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

	p.o.	i.v.
Diazepam	☐ mg	☐ mg
DikaliumchlrorazepaT	☐ mg	☐ mg
Haloperidol	☐ mg	☐ mg
Lorazepam	☐ mg	☐ mg
Midazolam	☐ mg	☐ mg
Promethazine	☐ mg	☐ mg
Other, specify:	☐ mg	☐ mg

M2 Non-opioids (pre-medication)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

	p.o.	i.v.	i.m.	supp.
Celecoxib	☐ mg	☐ mg	☐ mg	☐ mg
Diclofenac	☐ mg	☐ mg	☐ mg	☐ mg
Etoricoxib	☐ mg	☐ mg	☐ mg	☐ mg
Gabapentin	☐ mg	☐ mg	☐ mg	☐ mg
Ibuprofen	☐ mg	☐ mg	☐ mg	☐ mg
Ketoprofen	☐ mg	☐ mg	☐ mg	☐ mg
Ketorolac	☐ mg	☐ mg	☐ mg	☐ mg
Metamizol	☐ mg	☐ mg	☐ mg	☐ mg
Naproxen	☐ mg	☐ mg	☐ mg	☐ mg
Nefopam	☐ mg	☐ mg	☐ mg	☐ mg
Paracetamol (Acetaminophen)	☐ mg	☐ mg	☐ mg	☐ mg
Parecoxib	☐ mg	☐ mg	☐ mg	☐ mg
Pregabalin	☐ mg	☐ mg	☐ mg	☐ mg
Other, specify:	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐

Mark medications *given* to patient; record *cumulative* doses. PATIENT CODE:

PRE - MEDICATION

M3 Opioids & Clonidine (pre-medication)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

	Immediate release (PO & other)	Controlled release (PO & other)	i.v.	i.m.	supp.	s.c.
Buprenorphine	☐ mg	☐ µg\hr	☐ µg	☐ µg	☐ µg	☐ µg
Codeine	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Fentanyl	☐ µg transmucosal	☐ µg\hr transdermal	☐ µg	☐ µg	☐ µg	☐ µg
Hydrocodone	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Hydromorphone	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Morphine	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Nalbuphine	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Oxycodone	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Oxycodone (with Naloxon)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Pethidine (Meperidine)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Piritramide	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Tapentadol	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Tilidin (w\wo Naloxon)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Tramadol	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg
Other, specify:	☐	☐	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐	☐	☐
Clonidine	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg

SURGICAL PROCEDURE(S)

P1 Surgical procedure(s)

use ICD-9 codes link **http://icd9cm.chrisendres.com/index.php?action=procslist**

	ICD-9 Procedure Code		Text (only for your notes, not necessary for mask)
1		1	
2		2	
3		3	
4		4	

P2 Duration of surgery

Start surgery: Date: 2 0 1 Y M M D D Time: H H M M

End surgery: Date: 2 0 1 Y M M D D Time: H H M M

Mark medications *given* to patient; record *cumulative* doses.

PATIENT CODE:

INTRA-OPERATIVE

M4 General anaesthesia (intra-op)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

☐ Inhalational	☐ IV

M5 Regional anaesthesia (RA) (intra-op)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

☐ Epidural	☐ Spinal	☐ Brachial plexus	☐ Femoral
☐ Sciatic	☐ Paravertebral	☐ Other:	☐ Other:

In M8: Mark the RA medication(s) given in the RA column

M6 Non-opioids (intra-op)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

	i.v.	i.m.	supp.
Diclofenac	☐ mg	☐ mg	☐ mg
Ibuprofen	☐ mg	☐ mg	☐ mg
Ketamine	☐ mg	☐ mg	☐ mg
Ketoprofen	☐ mg	☐ mg	☐ mg
Ketorolac	☐ mg	☐ mg	☐ mg
Metamizol	☐ mg	☐ mg	☐ mg
Naproxen	☐ mg	☐ mg	☐ mg
Nefopam	☐ mg	☐ mg	☐ mg
Paracetamol (Acetaminophen)	☐ mg	☐ mg	☐ mg
Parecoxib	☐ mg	☐ mg	☐ mg
Other, specify:	☐	☐	☐
Other, specify:	☐	☐	☐
	i.v.	i.m.	supp.

Mark medications *given* to patient; record *cumulative* doses. PATIENT CODE:

INTRA-OP

M7 Wound infiltration (intra-op)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible; analgesic is not recorded):

☐ Single shot by surgeon ☐ Indwelling catheter ☐ Other, specify: ☐ Other, specify:

M8 Opioids & local anaesthetics & Clonidine (intra-op)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

	RA (see M5)	i.v.	i.m.	s.c.
Alfentanil	☐ µg	☐ µg	☐ µg	☐ µg
Buprenorphine	☐ µg	☐ µg	☐ µg	☐ µg
Codeine	☐ mg	☐ mg	☐ mg	☐ mg
Fentanyl	☐ µg	☐ µg	☐ µg	☐ µg
Hydrocodone	☐ mg	☐ mg	☐ mg	☐ mg
Hydromorphone	☐ mg	☐ mg	☐ mg	☐ mg
Morphine	☐ mg	☐ mg	☐ mg	☐ mg
Nalbuphin	☐ mg	☐ mg	☐ mg	☐ mg
Oxycodone	☐ mg	☐ mg	☐ mg	☐ mg
Pethidine (Meperidine)	☐ mg	☐ mg	☐ mg	☐ mg
Piritramid	☐ mg	☐ mg	☐ mg	☐ mg
Remifentanil	☐ µg	☐ µg	☐ µg	☐ µg
Sufentanil	☐ µg	☐ µg	☐ µg	☐ µg
Tramadol	☐ mg	☐ mg	☐ mg	☐ mg
Bupivacaine	☐	☐	☐	☐
Levobupivacaine	☐	☐	☐	☐
Lidocaine	☐	☐	☐	☐
Prilocaine	☐	☐	☐	☐
Ropivacaine	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐
Clonidine	☐ µg	☐ mg	☐ mg	☐ mg
	RA	i.v.	i.m.	s.c.

Mark medications *given* to patient; record *cumulative* doses. PATIENT CODE:

RECOVERY ROOM

M9 Non-opioids (recovery room)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

	p.o.	i.v.	i.m.	supp.
Celecoxib	☐ mg	☐ mg	☐ mg	☐ mg
Diclofenac	☐ mg	☐ mg	☐ mg	☐ mg
Etoricoxib	☐ mg	☐ mg	☐ mg	☐ mg
Gabapentin	☐ mg	☐ mg	☐ mg	☐ mg
Ibuprofen	☐ mg	☐ mg	☐ mg	☐ mg
Ketamine	☐ mg	☐ mg	☐ mg	☐ mg
Ketoprofen	☐ mg	☐ mg	☐ mg	☐ mg
Ketorolac	☐ mg	☐ mg	☐ mg	☐ mg
Metamizol	☐ mg	☐ mg	☐ mg	☐ mg
Naproxen	☐ mg	☐ mg	☐ mg	☐ mg
Nefopam	☐ mg	☐ mg	☐ mg	☐ mg
Paracetamol (Acetaminophen)	☐ mg	☐ mg	☐ mg	☐ mg
Parecoxib	☐ mg	☐ mg	☐ mg	☐ mg
Pregabalin	☐ mg	☐ mg	☐ mg	☐ mg
Other, specify:	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐
	p.o.	i.v.	i.m.	supp.

M10 Regional analgesia (recovery room)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

☐ Epidural	☐ Spinal	☐ Brachial plexus	☐ Femoral
☐ Sciatic	☐ Paravertebral	☐ Other:	☐ Other:

In M11: (1) Mark the RA medication(s) given in the RA column
(2) If the medication was given as PCA, tick appropriate box in the PCA column

Mark medications *given* to patient; record *cumulative* doses. PATIENT CODE:

RECOVERY ROOM

M11 Opioids & local anaesthetics & Clonidine (recovery room)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible)

	Immediate release (PO & other)	Controlled release (PO & other)	RA (see M10)	i.v.	i.m.	supp.	s.c.	PCA (see M10)
Buprenorphine	☐ mg	☐ µg\hr	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐
Codeine	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Fentanyl	☐ µg transmucosal	☐ µg\hr transdermal	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐
Hydrocodone	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Hydromorphone	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Morphine	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Nalbuphin	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Oxycodone	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Oxycodone (with Naloxone)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Pethidine (Meperidine)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Piritramid	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Sufentanil	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐
Tapentadol	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Tilidin (w\wo Naloxon)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Tramadol	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Bupivacaine	☐	☐	☐	☐	☐	☐	☐	☐
Levobupivacaine	☐	☐	☐	☐	☐	☐	☐	☐
Lidocaine	☐	☐	☐	☐	☐	☐	☐	☐
Prilocaine	☐	☐	☐	☐	☐	☐	☐	☐
Ropivacaine	☐	☐	☐	☐	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐	☐	☐	☐	☐
Clonidine	☐ µg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Naloxone (only as an antagonist for respiratory depression)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
	Immediate release (PO & other)	Controlled release (PO & other)	RA	i.v.	i.m.	supp.	s.c.	PCA

Mark medications *given* to patient; record *cumulative* doses. PATIENT CODE:

WARD

M12 Non-opioids (ward)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

	p.o.	i.v.	i.m.	supp.
Celecoxib	☐ mg	☐ mg	☐ mg	☐ mg
Diclofenac	☐ mg	☐ mg	☐ mg	☐ mg
Etoricoxib	☐ mg	☐ mg	☐ mg	☐ mg
Gabapentin	☐ mg	☐ mg	☐ mg	☐ mg
Ibuprofen	☐ mg	☐ mg	☐ mg	☐ mg
Ketamine	☐ mg	☐ mg	☐ mg	☐ mg
Ketoprofen	☐ mg	☐ mg	☐ mg	☐ mg
Ketorolac	☐ mg	☐ mg	☐ mg	☐ mg
Metamizol	☐ mg	☐ mg	☐ mg	☐ mg
Naproxen	☐ mg	☐ mg	☐ mg	☐ mg
Nefopam	☐ mg	☐ mg	☐ mg	☐ mg
Paracetamol (Acetaminophen)	☐ mg	☐ mg	☐ mg	☐ mg
Parecoxib	☐ mg	☐ mg	☐ mg	☐ mg
Pregabalin	☐ mg	☐ mg	☐ mg	☐ mg
Other, specify:	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐
	p.o.	i.v.	i.m.	supp.

M13 Regional analgesia (ward)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

☐ Epidural	☐ Spinal	☐ Brachial plexus	☐ Femoral
☐ Sciatic	☐ Paravertebral	☐ Other:	☐ Other:

In M14: (1) Mark the RA medication(s) given in the RA column
(2) If the medication was given as PCA, tick appropriate box in the PCA column

Mark medications *given* to patient; record *cumulative* doses. PATIENT CODE:

WARD

M14 Opioids & local anaesthetics & Clonidine (ward)

☐ yes ☐ no ☐ not possible to obtain the information

If yes, which (multiple answers possible):

	Immediate release (PO & other)	Controlled release (PO & other)	RA (see M13)	i.v.	i.m.	supp.	s.c.	PCA (see M13)
Buprenorphine	☐ mg	☐ µg\hr	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐
Codeine	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Fentanyl	☐ µg transmucosal	☐ µg\hr transdermal	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐
Hydrocodone	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Hydromorphone	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Morphine	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Nalbuphin	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Oxycodone	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Oxycodone (with Naloxone)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Pethidine (Meperidine)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Piritramid	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Sufentanil	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐ µg	☐
Tapentadol	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Tilidin (w\wo Naloxon)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Tramadol	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Bupivacaine	☐	☐	☐	☐	☐	☐	☐	☐
Levobupivacaine	☐	☐	☐	☐	☐	☐	☐	☐
Lidocaine	☐	☐	☐	☐	☐	☐	☐	☐
Prilocaine	☐	☐	☐	☐	☐	☐	☐	☐
Ropivacaine	☐	☐	☐	☐	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐	☐	☐	☐	☐
Clonidine	☐ µg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
Naloxone (only as an antagonist for respiratory depression)	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐ mg	☐
	IR	CR	RA	i.v.	i.m.	supp.	s.c.	PCA

M15 Measurement of pain: Was pain documented as defined in the SOPs?

☐ yes ☐ no ☐ not possible to obtain the information

Appendix 2

PATIENT OUTCOMES QUESTIONNAIRE

Dear Sir \ Madam

We would be grateful if you would participate in our survey on how patients feel after surgery. The aim of the survey is to improve the management of pain after surgery in this department.

Your participation is voluntary and the information you provide will be made anonymous once you hand in this questionnaire. This means that your name or other form of identification will be deleted from the questionnaire after you hand it in and will not be included in any records we will hold.

Your answers in this questionnaire will **not** be shared with your medical or nursing team.

Your team will treat you in the same way whether or not you choose to participate in our survey.

Many thanks for considering to take part in this survey.

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PATIENT CODE:

PATIENT OUTCOMES QUESTIONNAIRE

The following questions are about pain you experienced since your surgery.

P1. On this scale, please indicate the **worst pain** you had since your surgery:

0	1	2	3	4	5	6	7	8	9	10

no pain **worst pain possible**

P2. On this scale, please indicate the **least pain** you had since your surgery:

0	1	2	3	4	5	6	7	8	9	10

no pain **worst pain possible**

P3. How often were you in **severe pain** since your surgery?
Please circle your best estimate of the percentage of time you experienced **severe pain**:

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

never in severe pain **always in severe pain**

P4. Circle the one number below that best describes how much, since your surgery, **pain interfered with or prevented you from** ...

a. doing **activities in bed** such as turning, sitting up, changing position:

0	1	2	3	4	5	6	7	8	9	10

did not interfere **completely interfered**

b. **breathing deeply** or **coughing**:

0	1	2	3	4	5	6	7	8	9	10

did not interfere **completely interfered**

c. **sleeping**:

0	1	2	3	4	5	6	7	8	9	10

did not interfere **completely interfered**

d. Have you been **out of bed** since your surgery?

☐ Yes ☐ No

If yes, how much did **pain interfere or prevent you from doing activities out of bed** such as walking, sitting in a chair, standing at the sink:

0	1	2	3	4	5	6	7	8	9	10

did not interfere **completely interfered**

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PATIENT CODE:

PATIENT OUTCOMES QUESTIONNAIRE

P5. Pain can affect our mood and emotions.
On this scale, please circle the one number that best shows how much, since your surgery, **pain caused you to feel** ...

a. **anxious**

0	1	2	3	4	5	6	7	8	9	10
not at all										**extremely**

b. **helpless**

0	1	2	3	4	5	6	7	8	9	10
not at all										**extremely**

P6. Have you had any of the following **side effects** since your surgery?
Please circle "0" if no; if yes, circle the one number that best shows the severity of each:

a. **Nausea**

0	1	2	3	4	5	6	7	8	9	10
none										**severe**

b. **Drowsiness**

0	1	2	3	4	5	6	7	8	9	10
none										**severe**

c. **Itching**

0	1	2	3	4	5	6	7	8	9	10
none										**severe**

d. **Dizziness**

0	1	2	3	4	5	6	7	8	9	10
none										**severe**

P7. Since your surgery, how much **pain relief** have you received?
Please circle the one percentage that best shows how much relief you have received from all of your **pain treatments** combined (medicine and non-medicine treatments):

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
no relief										**complete relief**

P8. Would you have liked **MORE pain treatment** than you received?

☐ Yes ☐ No

P9. Did you receive any **information** about your **pain treatment** options?

☐ Yes ☐ No

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PATIENT CODE:

PATIENT OUTCOMES QUESTIONNAIRE

P10. Were you **allowed to participate in decisions** about your **pain treatment** as much as you wanted to?

0	1	2	3	4	5	6	7	8	9	10

not at all **very much so**

P11. Circle the one number that best shows how **satisfied** you are with the results of your **pain treatment** since your surgery:

0	1	2	3	4	5	6	7	8	9	10

extremely dissatisfied **extremely satisfied**

P12. Did you use or receive any **non-medicine methods** to relieve your **pain**?

☐ Yes ☐ No

If yes, **check all** that apply:

☐ cold pack ☐ meditation ☐ deep breathing
☐ heat ☐ acupuncture ☐ prayer
☐ talking to medical staff ☐ walking ☐ massage
☐ talking to friends or relatives ☐ relaxation ☐ imagery or visualization
☐ TENS (Transcutaneous Electrical Nerve Stimulation)
☐ distraction (like watching TV, listening to music, reading)
☐ other (please describe):

P13. Did you have a **persistent painful condition for 3 months** or more before coming into hospital for this surgery?

☐ Yes ☐ No

a. If yes, **how severe** was the **pain** most of the time? Please circle the number that indicates this.

0	1	2	3	4	5	6	7	8	9	10

no pain **worst pain possible**

b. If yes, **where** was this **persistent pain** located?

☐ site of surgery ☐ elsewhere ☐ both (site of surgery and elsewhere)

Thank you for your time and feedback

To be filled in by the research assistant Research assistant code:

Patient was interviewed: ☐ Yes ☐ No

If yes, please mark the reason(s):

☐ Too ill / weak ☐ Too much pain ☐ Requested assistance ☐ Did not understand scales
☐ Technical reasons (patient has no eyeglasses / is blind; can not sit up; is illiterate; arm is in cast; etc)

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