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Enrollment challenges in multi-center, international studies: the example of the GAS trial

Abbreviated Title: Enrollment challenges in the GAS trial

Research Report

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MeSH-compliant keywords: Anesthesia, General; Anesthesia, Spinal; Parental consent; Randomized Controlled Trials; Child

What is already known: There is a perception that it is difficult to recruit children to participate in randomized controlled trials. The overall enrollment rate in the General Anesthesia compared to Spinal anesthesia (GAS) trial was 18%.

What this article adds: The predominant reasons for low enrollment in the GAS trial varied by country. Particularly striking were the high rate of U.S. surgeon refusals as well as high rates of parental refusal in the USA, Australia, and the Netherlands.

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Abstract:

Introduction: Randomized trials are important for generating high quality evidence, but are perceived as difficult to perform in the pediatric population. Thus far there has been poor characterization of the barriers to conducting trials involving children, and the variation in these barriers between countries remains undescribed. The General Anesthesia compared to Spinal anesthesia (GAS) trial, conducted in 7 countries between 2007-2013, provides an opportunity to explore these issues.

Methods: We undertook a descriptive analysis to evaluate the reasons for variation in enrollment between countries in the GAS trial, looking specifically at the number of potential subjects screened, and the subsequent application of four exclusion criteria that were applied in a hierarchical order.

Results: A total of 4023 patients were screened by 28 centers in 7 countries. Australia and the USA screened the most subjects, accounting for 84% of all potential trial participants. Enrollment per country ranged from a low of 24 in New Zealand to a high of 210 in Australia. The percentage of subjects eliminated from the screened pool by each exclusion criterion varied between countries. Exclusion due to a predefined condition (H1) eliminated only 5% of potential subjects in Italy and the UK, but 37% in Canada. Exclusions due to a contraindication or a physician's refusal most impacted enrollment in Australia and the USA. The patient being "too large for spinal anesthesia" was the most commonly cited by anesthetists who refused to enroll a patient (64% of anesthetist refusals). The majority of surgeon refusals came from the U.S.A., where surgeons preferred the patient to receive a general anesthetic. The percentage of approached parents refusing to consent ranged from a low of 3% in Italy to a high of 70% in the USA and Netherlands. The most frequently cited reason for parent refusal in all countries was a preference for general anesthesia (median: 43%, range: 32-67%). However, a sizeable proportion of parents in all countries had a contrasting preference for spinal anesthesia (median: 25%, range: 13-31%), and 23% of U.S. parents expressed concern about randomization.

Conclusion: The GAS trial highlights enrollment challenges that can occur when conducting multi-center, international, pediatric studies. Investigators planning future trials should be aware of potential differences in screening processes across countries, and that exclusions by anesthetists and surgeons may vary in reason, in frequency, and by country. Furthermore, investigators should be aware that the U.S. centers encountered particularly high surgeon and parental refusal rates and that U.S. parents were uniquely concerned about randomization. Planning trials that address these difficulties should increase the likelihood of successfully recruiting subjects in pediatric trials.

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Introduction:

The General Anesthesia compared to Spinal anesthesia (GAS) trial aimed to evaluate the effect of general anesthesia on long-term brain development using an "international, multisite, randomized, controlled, equivalence trial" assessing "awake-regional anesthesia versus general anesthesia in infants undergoing inguinal herniorrhaphy," and was conducted in 28 hospitals in 7 countries. Recruitment occurred between Feb. 9, 2007 and Jan. 31, 2013. The primary outcome of the trial will be a neurodevelopmental assessment at 5 years of age using the Weschler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient. The secondary outcomes were the composite cognitive score of the Bayley Scales of Infant and Toddler Development, completed at 2 years of age, and the incidence of apnea in the early post-operative period. These secondary outcomes have been published.[1,2] Secondary outcomes at 5 years will include a pediatric assessment, NEPSY TASKS evaluating visual and auditory attention and Behavioral Rating of Executive Function (BRIEF).

In the course of evaluating and reporting these data, study investigators noted that enrollment rates varied widely by country and that the overall enrollment rate was 18%.

Clinical trials are important for pediatric medicine as they provide high quality evidence. There is a perception that pediatric trials are difficult to perform due to a reluctance of families and physicians to participate.[3,4,5] It is also thought that enrollment rates may vary between countries. However, there are few studies that have tested these perceptions. The GAS trial provides an opportunity to explore enrollment patterns that may inform the design and conduct of future trials in children. We performed a descriptive analysis of enrollment data to identify factors potentially responsible for the differences in enrollment observed across countries participating in the GAS trial.

Methods:

This secondary analysis of collected data was approved by the Trial Steering Committee. The study biostatisticians at Murdoch Children's Research Institute (Victoria, Australia) provided access to the enrollment database.

The GAS study protocol can be found on-line at http://www.thelancet.com/protocol-reviews/09prt9078. In brief, eligible subjects were identified "from operating room schedules or at preadmission clinics and recruited in the clinic or in the preadmission areas of the operating floor." Eligible patients were infants up to 60 weeks post-menstrual age who had been born at greater than 26

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weeks gestation, scheduled for unilateral or bilateral inguinal herniorrhaphy. Exclusion criteria were then applied in a hierarchical order: (1) presence of pre-determined exclusion criteria (a history of congenital heart disease requiring surgery or pharmacotherapy, mechanical ventilation immediately before surgery, known chromosomal abnormalities or other congenital abnormalities that could affect neurodevelopment, previous exposure to volatile anesthetics or benzodiazepines as a neonate or in the third trimester in utero, the presence of known neurological injury, social or demographic factors that might make follow-up difficult, or having a primary language spoken at home in which neurodevelopmental tests were not available); (2) contraindication to general or regional anesthesia; or surgeon, anesthetist, or other physician refusal to participate; (3) parental refusal to consent; and (4) other reasons for not randomizing (largely logistical reasons).[1] Within hierarchy 1, the presence of any exclusion criterion could halt the collection of further data in that category. Similarly, in hierarchy 2, the refusal of any physician involved could halt the enrollment process, although in some cases the opinions of other involved physicians were sought before a refusal was encountered. Thus, the distributions within each hierarchy are unlikely to represent true numbers given the incomplete nature of data collection once a subject was excluded; it is for this reason that exclusions were pooled in each hierarchy.

Descriptive statistical analysis of eligibility and enrollment data was performed using STATA 12 (College Station, TX). We evaluated the application of each exclusion criterion in the study overall and in each country. For the second and third exclusion criteria (provider refusal to participate and parent refusal to consent, respectively), we tabulated the reasons for refusal that were collected by the original investigators.

Results:

Overall screening and enrollment:

Screening and exclusion totals are presented in Figure 1. Twenty-eight centers in 7 countries participated. Note that centers with different caseloads joined the trial at different time points. Four exclusion criteria (H1-H4) were applied in a hierarchical order (Figure 1). Australia and the USA screened the most potential subjects, (1477 and 1882, respectively), accounting for 84% of all screened potential subjects. (For screening trends, see Supplemental Figure S1 and S2). Overall, only 18% (n=722) of screened subjects were ultimately enrolled in the study. Australia, Italy and the USA contributed the greatest numbers of participants (n= 210, 165, and 148, respectively), while New Zealand contributed

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the smallest number to the total (n=24). (For enrollment over time, see Supplemental Figure S3). The percent of subjects enrolled out of the total number screened varied by country, ranging from a low of 8% in the USA to a high of 88% in Italy (Table 1).

Application of the first exclusion criterion (Hierarchy 1): pre-defined conditions warranting exclusion

Overall, 27% (1085) of screened subjects were excluded due to the presence of pre-defined conditions and/or not meeting age criteria (Figure 1). The proportions of screened subjects eliminated due to H1, by country, were 28% in Australia, 37% in Canada, 5% in Italy, 13% in New Zealand, 5% in the Netherlands, 9% in the UK, and 31% in the U.S.A. (Table 2). The most frequently recorded exclusion criteria in this category were language differences (n=255) and previous exposure to a volatile anesthetic or benzodiazepine (n=255).

Application of the second exclusion criterion (Hierarchy 2): contraindication to spinal or general anesthesia; or, refusal by anesthetist, surgeon, or other physician to enroll subject

Within this category, the presence of any one of these factors excluded the child, but for some subjects more than one item was recorded. Across all sites, 1084 potential subjects were excluded in Hierarchy 2 (Figure 1). Contraindications to spinal anesthesia or general anesthesia were logged for 172 subjects excluded at this stage. There were 506 instances of anesthetist refusals, 414 instances of surgeon refusals, and 52 instances of other involved physicians refusing to randomize a subject. Provider refusals eliminated a disproportionate number of subjects in Australia and the USA compared to other countries; over 40% of remaining eligible subjects were eliminated in Australia and the USA due to provider refusals, compared to rates of ≤13 % in all other countries. Surgeon refusals occurred almost entirely in the USA (n=357) while the highest number of anesthetist refusals came from Australia (n=301), followed by the USA (n=174) and the Netherlands (n=15) (Figure 2).

The most common contraindications recorded were: the child being too large for a spinal anesthetic (124), having other surgical procedures at the same time (19), medical complexity (15), case delay of >2 hours (5), concern for spine anomalies or tethered cord (5), surgical complexity (4), concern for coagulopathy (4), and a plan for laparoscopy (4).

This analysis revealed that exclusions due to the child being “too large for spinal anesthesia” were variably coded as contraindications or anesthetist refusals. In total, 457 infants were excluded based on size, yet the weight cutoff that was considered too large was not uniformly agreed-upon across

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countries. The majority of size exclusions came from Australian sites (66%), with the USA accounting for another 31% of size exclusions. The application of different weight cutoffs is reflected by the maximum weight of children enrolled by country. The maximum weight enrolled in New Zealand it was 5.3 kg, and in Australia it was 6.9 kg. On the other end of the spectrum, the maximum weights enrolled in the Netherlands and in the UK were 8.1 kg and 8.2 kg, respectively. Mean, maximum, and minimum weights of enrolled subjects are shown in Supplemental Figure S4.

The reasons behind provider refusals to enroll subjects were explored. For anesthetist refusals, the most frequent reason given was that the child was too large for a spinal (n= 266), followed by "other" miscellaneous reasons (n= 41), a preference for general anesthesia (GA, n= 26) preference for spinal (n= 25), or too many comorbidities (n=22), (Figure 3). There were 414 instances of surgeons refusing to enroll a subject, 86% of which came from U.S. surgeons. The most common reason surgeons refused was a "preference for general anesthesia" (n=336) (Figure 3), with US surgeons providing this reason in 323 cases. Although the study methods did not capture what proportion of *excluded* subjects were scheduled for bilateral repairs or laparoscopic approaches, among enrolled subjects, the USA had the most subjects who underwent a laparoscopic inspection of the contralateral side (n=24, 42% of all "other" procedures performed in the USA). By contrast, there were only 2 laparoscopic inspections in Italy, and 1 in both the UK and Canada, and no laparoscopic inspections in the other countries (data not shown). The USA did not have the highest rate of bilateral hernias among the participating countries. In Australia, 83% of enrolled subjects had bilateral hernias; in Canada, 73%; and in the USA, 52% (data not shown).

Application of the third exclusion criterion (Hierarchy 3): parents refusing to consent

Parents of 1522 remaining potential subjects were approached and 50% agreed to participate. By country, the rates of refusal varied widely, from a low of 3% in Italy to a high of 70% in the USA and 69% in the Netherlands (Figure 4). Of the 765 parental refusals, 649 of them provided reasons that were common and therefore easily tabulated. Considering all sites together, the most common reasons parents gave for not wanting to participate were "wanting a general anesthetic" (n=249, 39%) and "wanting a spinal anesthetic" (n=151, 23%). Although the absolute numbers varied by sample size, this distribution of reasons was similar across all centers. Of note, parents in the USA also expressed "not wanting to be randomized" with a frequency of 23%, on par with the frequency of having a strong preference for GA (32%) or spinal anesthesia (20%), (U.S. data only). Parents in other countries less frequently indicated that their refusal hinged on the issue of randomization. There were parents who

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refused to participate because they did not want to follow up (n= 41, 6%), specifically, in the USA (n=21), Australia (n=11), the Netherlands (n=7), Italy (n=1), and New Zealand (n=1).

Discussion:

The overall enrollment rate of 18% in the GAS trial demonstrates that subject recruitment and enrollment can be difficult in multicenter, international studies. The large variation in enrollment rates across countries, however, suggests that these clinical environments were not uniformly conducive to participation in clinical research. As a secondary analysis, this investigation remains descriptive and cannot attribute causality for specific enrollment challenges. However, one cannot ignore that enrollment efforts in the USA in particular were hindered by a high rate of surgeon and parental refusals. By contrast, in Italy and the United Kingdom there were very few subject exclusions in these categories. We recognize that this analysis reflects attitudes and practices of the centers agreeing to participate in the GAS trial, yet may not be reflective of all centers within each country. For a center to enroll, anesthetists had to feel there was reasonable equipoise between regional and general anesthetic techniques. At centers where one method was predominant, providers may have been concerned that offering the alternative was either unethical (*e.g.* given their belief in the superiority of one technique over the other), or unfeasible (*e.g.* if they knew the operations would last longer than the duration of a spinal anesthetic). With these caveats in mind, our analysis suggests that the first three hierarchies eliminated subjects disproportionately at different sites.

We first evaluated differences in numbers of potential subjects screened and exclusion based on pre-defined criteria. It is worth noting that the imbalance in potential subjects screened between different countries resulted in part from centers entering the study at different time points, differing numbers of participating centers per country, and the centers having different caseloads. As a result, the rate of screening varied both across countries and within each country over time (See Supplemental Figures S1 and S2).

However, we noted that the proportion of screened subjects excluded due to Hierarchy 1 varied widely across countries, (e.g. 5% in Italy and the UK vs. 37% in Canada, 31% in the USA, and 28% in Australia). This amount of variation was surprising given that the Hierarchy 1 criteria were clear and predetermined. Based on the information we have, we can only hypothesize possible reasons for these differences. One potential explanation is that the populations served by the study hospitals in the various countries are different. Another possibility is that in centers with a low Hierarchy 1 exclusion

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rate, investigators were aware of the presence of exclusion criteria, and only considered enrolling patients who did not have obvious pre-defined exclusion criteria. Such pre-screening may have seemed necessary based upon the limited resources some centers may have had, as it would have made recruitment efforts more efficient. However, when screening practices are not consistent, questions arise about the generalizability of the data and the introduction of selection bias into the study sample.

In the second exclusion hierarchy, we discovered that many infants were excluded because they were "too large for spinal anesthesia," yet size was not listed as an official reason for exclusion in the Case Report Form nor did sites agree on what weight was "too large." In the Australian sites, this cutoff was left to the discretion of the anesthetists, and children were excluded for weights ranging from 4-6 kg. In the USA, children > 6 kg were generally considered too large. The high percentage of size exclusions out of Australia is probably explained by the employment of a more conservative weight cut-off. Of note, while there was a perception that spinal placement was more difficult in larger babies, there was no evidence that patient weight was a predictor of regional anesthesia failure in the GAS trial.[6] The mean weight of children with successful regional was 4.37 kg, as compared to 4.18 kg among children who had a regional anesthetic failure.

Provider refusals were apparently not a barrier in most of the countries except for Australia and the USA. Anesthetists tended to exclude babies that were felt to be too large for spinal anesthesia, whereas surgeon refusals were most often due to a preference for general anesthesia. The disproportionate number of surgeon refusals in the USA was striking. This may reflect that infant spinal anesthesia is not routine in the USA as a whole, and therefore many surgeons are uncomfortable with it. Similarly, surgeons may have been concerned about operating within time constraints inherent to spinal anesthesia and/or that it would have a negative impact on surgical trainee teaching.[7] All of the participating centers were training institutions. A plan for laparoscopic inspection of the contralateral side may have driven U.S. surgeons' preferences for GA.

Parental consent rates varied widely, with only 30% of those U.S. parents approached agreeing to participate, compared to 97% of Italian parents approached. This may reflect different consent processes, different cultural norms and values (i.e. whether patient/parent autonomy or physician authority is more highly valued), and the lay public's attitudes about research in general. There is scant literature available to confirm these potential explanations. In a qualitative study of the "hidden curriculum" in Italian medical training, themes that emerged included (1) the physician's role to reassure and protect patients, *e.g.* by limiting the information that is conveyed, and not conveying uncertainty,

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and (2) that a power differential exists between physicians and patients, *e.g.* patients have an attitude of deference and submission towards the physician.[8] In a 2004 paper, Surbone *et al.* claimed that the practices of obtaining informed consent and disclosing diagnostic and prognostic information were different in Italy compared to the UK and USA.[9] Another study of ICU physicians in Europe found that only a minority of the Italian doctors in their cohort supported full disclosure of medical information to their patients.[10] While these findings are not directly applicable to the trends observed in the GAS trial, they do suggest that cultural differences may influence the way informed consent is regarded and approached by both physicians and patients in different countries.

Despite the differing consent rates, the parents' reasons for refusal were fairly similar from country to country. The most common reason parents did not consent was because they had a preference for anesthetic type. In the USA, a sizeable proportion of parents indicated that their primary concern was that their child would be randomized. Other studies investigating the characteristics of people who do or do not consent to participate in clinical research have also found that "concrete preferences" and discomfort with randomization are common among those who refuse to participate in clinical research.[11,12] We do not know what aspects of randomization caused parents discomfort in this study. However, parental responses to the prospect of randomization have been investigated in other clinical trials. The purpose and method of randomization are often misunderstood by parents.[5,13] Also, some parents fear their child will be randomized to the "less effective" arm of a study,[13] and some perceive that randomization limits treatment options and removes parental control over decisions.[14] In addition, adults have expressed concerns that randomization in the clinical research setting compromises the individualized care that they otherwise expect from their physician.[15] Adults have expressed concern that randomization interferes with physician autonomy to make decisions on the patient's behalf and/or compromises the collaborative nature of the physician-patient relationship.[15] Similarly, parents of children with hydronephrosis and urologists reported discomfort with the element of chance inherent in randomization when it came to surgical intervention trials; parents expressed a preference to participate in prospective cohort studies in which parents and surgeons could make treatment decisions jointly.[3] What can be concluded from the GAS trial is that when anesthetic options exist, many parents want to participate in the decision.

Prior work in the perioperative research setting has demonstrated that parents' assessment of the risk/benefit ratio often distinguishes those who consent from those who refuse; parents who consent for their child to participate in research tend to assess the risk/benefit ratio of study participation as

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lower (i.e. more favorable) as compared to parents who do not consent.[16] And it is worth noting that a child's illness severity can contribute to parents' assessment of risks and benefits. In a study of hypothetical research scenarios, parents of newborns in the ICU were more likely to enroll their baby in a trial that involved moderate risk and possible major direct benefit, compared to parents of healthy newborns.[17] Perhaps this phenomenon played a role in the GAS trial, given the relatively good health of babies that were eligible. Although parental perception of risks likely contributed to their preferences for a particular type of anesthesia, concern about risks was not among the explicitly mentioned reasons parents gave for declining.

Limitations:

Given that this was a secondary analysis of pre-existing data, we were only able to engage in a descriptive analysis of subject enrollment. Reasons for enrollment differences between countries cannot be fully explored with this limited data set. Furthermore, we were only able to quantitatively analyze the most commonly cited reasons that patients were excluded or that providers refused to participate. We can make conjectures about parental and provider attitudes that drove their refusals, but without in-depth interviews no conclusions about attitudes or values can be drawn. The writing of this paper prompted several additional questions regarding whether cultural differences could explain different rates of physician and parent refusal, whether differences in hospital acuity influenced the number of potentially eligible patients, and if or how parental socioeconomic factors contributed to parental consent rates, and how that could have implications for subject neurocognitive testing at 2 and 5 years. We were unable to adequately address these questions with the available data but recognize their value for future research.

Broader implications:

This study confirmed that many children need to be screened to achieve adequate participation rates in some trials. While the rate will depend partly on the nature of the exclusion criteria, these findings demonstrate that when planning large trials involving children, researchers should carefully collect prevalence data, run pilot studies to see if recruitment targets can be met, and ensure that screening is uniform across sites. Defining screening criteria for all participating centers to eliminate "prescreening" would improve confidence in generalizability. Also, assumptions based on pilot data collected in one country may not be applicable to other countries.

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Given that surgeon refusal was a major contributor to subject exclusion, it may be prudent in future U.S. studies to include surgeons as co-investigators, to increase their interest and stake in a trial's success. Our findings also reinforce the value of multicenter trials, in that slow recruitment in one country may be offset by more rapid recruitment in another.

Conclusion:

In this secondary analysis we have examined factors that contributed to a low overall enrollment rate, and highly variable enrollment by country, in the GAS trial. For future studies comparing anesthetic techniques, investigators should be prepared to contend with, in particular, surgeon and parental attitudes about anesthesia and randomization that may hinder recruitment into a research study.

ETHICS: This secondary analysis was approved by the GAS trial steering committee. No additional ethics approval was required given that data was de-identified.

FUNDING: This secondary analysis was generously funded with departmental resources.

DISCLOSURES:

Sarah Arnup – GAS Trial Investigator

Andrew Davidson – Editor, Pediatric Anesthesia; GAS Trial Investigator; GAS Trial Steering Committee

Jurgen C. de Graaff – Associate Editor, Pediatric Anesthesia; GAS Trial Investigator; GAS Trial Steering Committee

Nicola Disma – GAS Trial Investigator; GAS Trial Steering Committee

Liam Dorris – GAS Trial Investigator; GAS Trial Steering Committee

Katherine Gentry – Nothing to disclose

Agnes Hunyady – GAS Trial Investigator

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Figure Captions:

Figure 1: GAS Trial Enrollment

Figure 2: Provider Refusal by Country

Figure 3: Reasons for Provider Refusal

Figure 4: Parental Consent and Refusal

Table 1

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Country	Subjects Screened (n)	Subjects Enrolled (n)	Percent enrolled out of total screened (%)
Australia	1477	210	14
USA	1882	148	8
Canada	136	50	37
NZ	46	24	52
UK	97	84	87
Italy	188	166	88
Netherlands	197	40	20
Total	4023	722	18

Table 2: Exclusion due to pre-determined criteria (H1)

Country	Number of subjects excluded due to H1 (n)	Percent of each country's screened subjects excluded by H1
Australia	415	28
USA	583	31
Canada	50	37
NZ	6	13
UK	5	5
Italy	9	5
Netherlands	17	9
All Countries	1085	27

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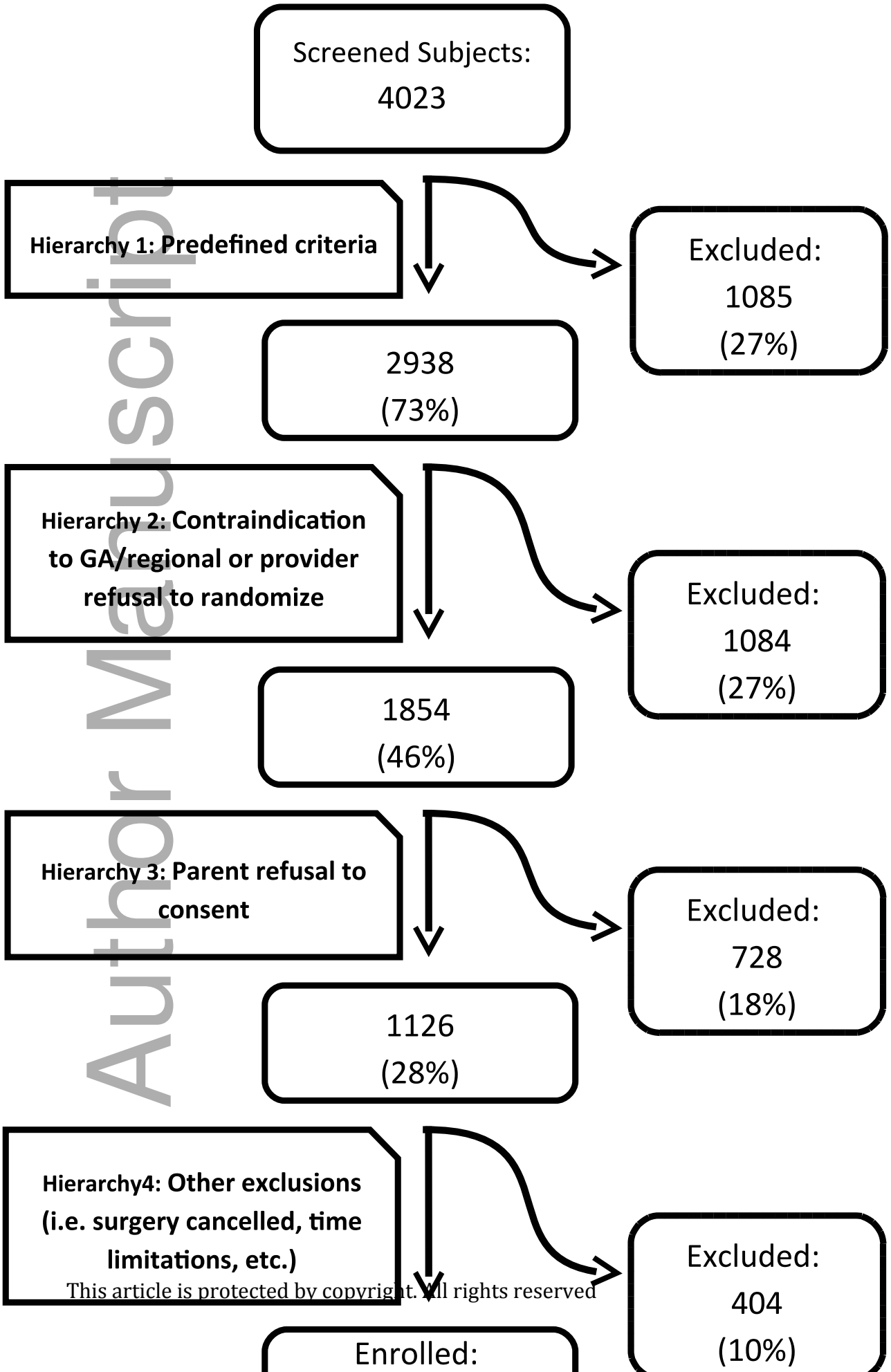

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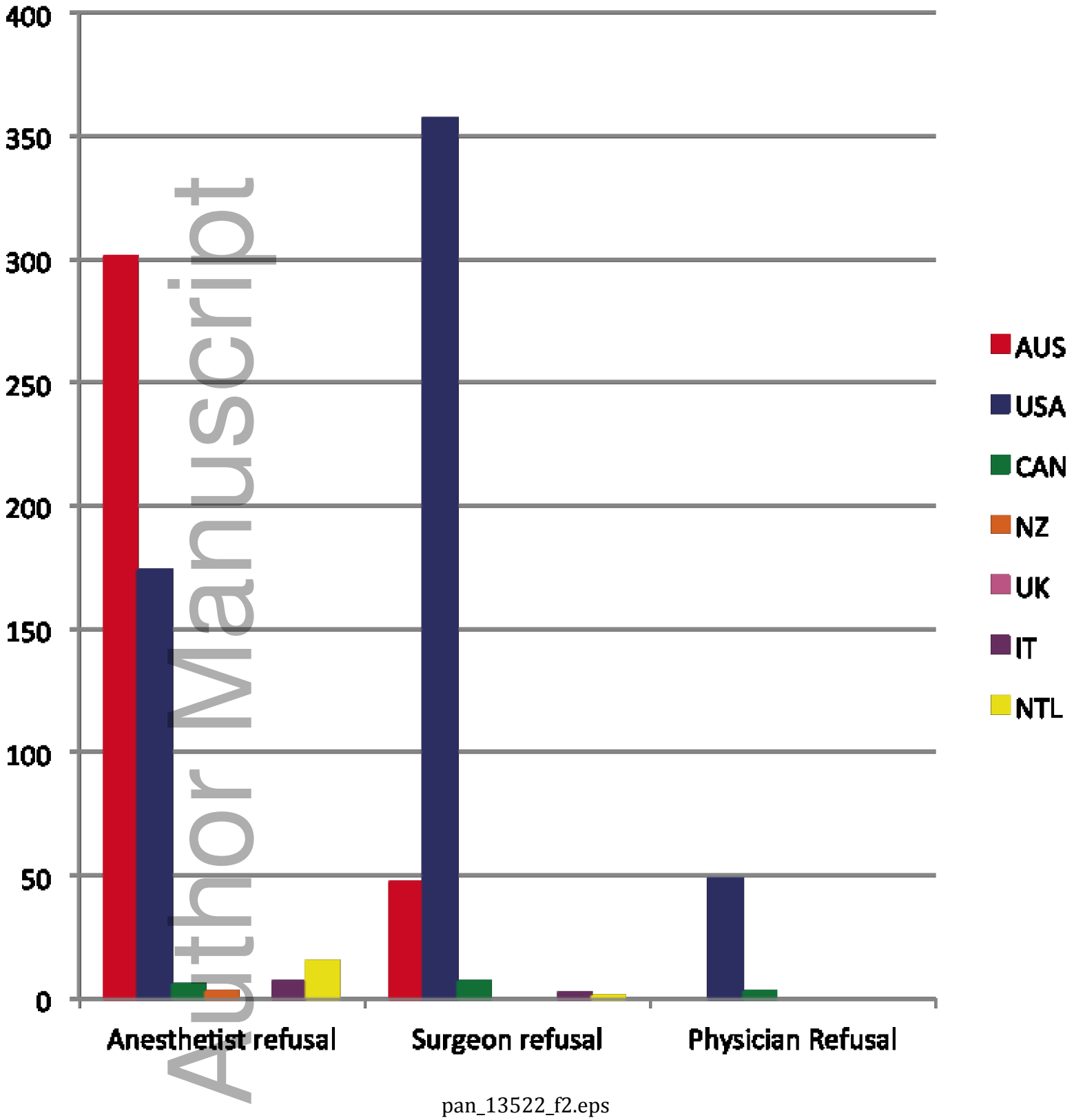

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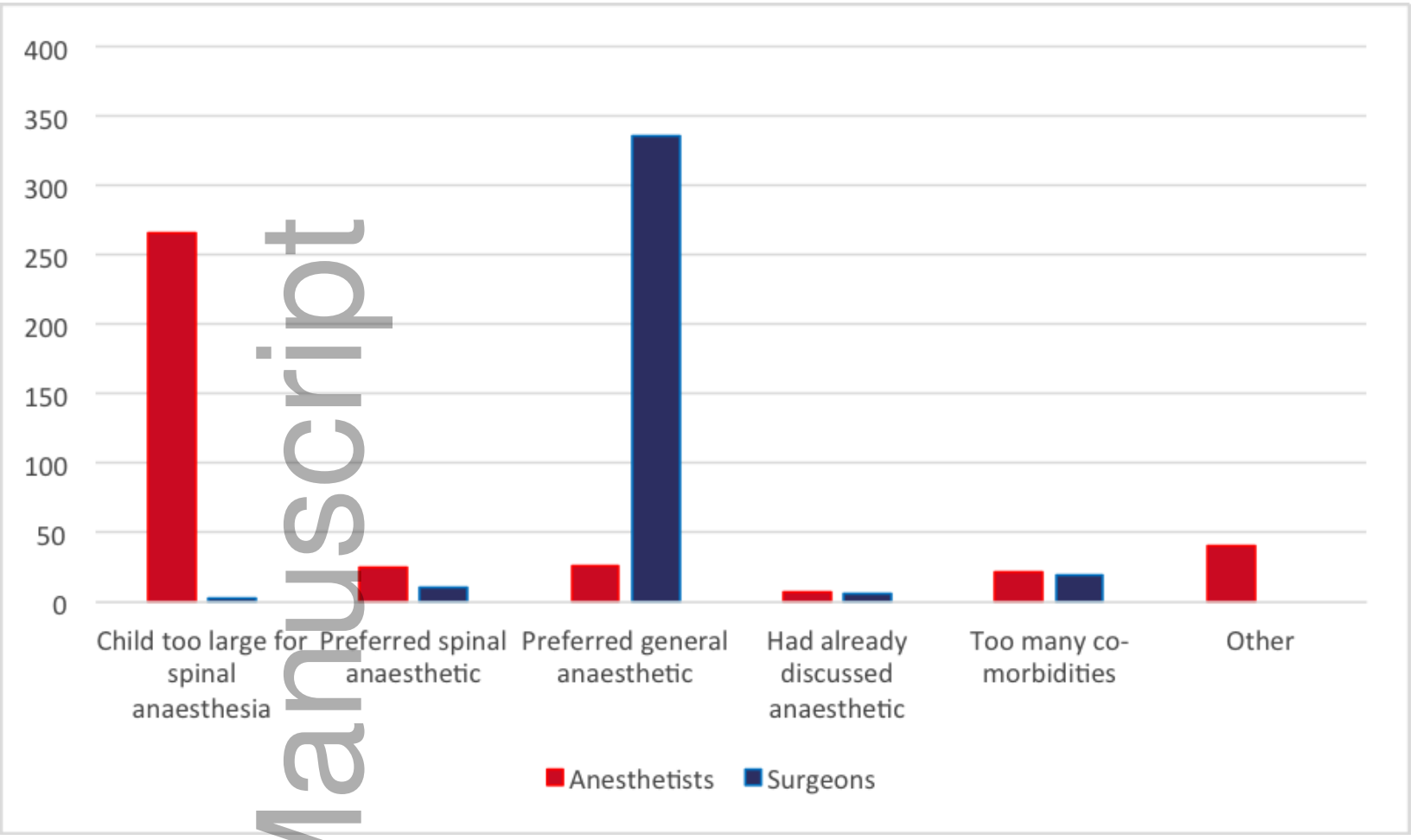

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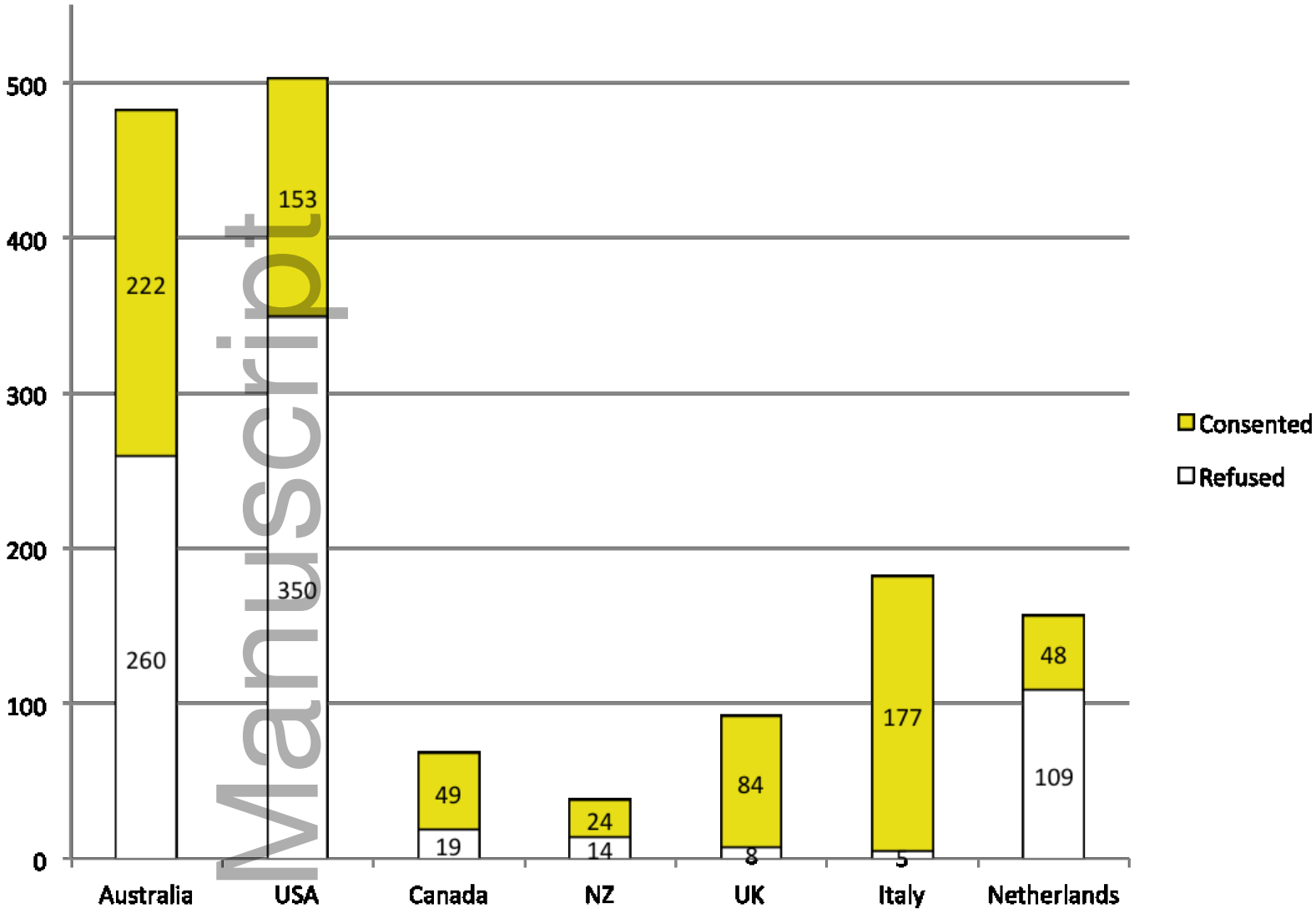

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