1. TITLE

Prospective, open, non-controlled, single-arm post-market clinical follow-up investigation to confirm the safety and performance of the SAFIRA system in ultrasound guidance and/or nerve stimulation peripheral nerve block.

1.1 Short Title

The SAFIRA PMCF Study.

2. INTRODUCTION AND BACKGROUND

A 'single-injection' or 'one-shot' peripheral nerve block (PNB) is a form of regional anaesthesia where a local anaesthetic (LA) is precisely administered, via a needle attached to a syringe, around a peripheral nerve or a group of peripheral nerves in order to temporarily block the transmission of nerve impulses to numb all or part of a limb in order to allow certain surgical procedures without the need for a general anaesthetic and which provides a numbing effect of between 4 – 16 hours (depending upon the LA used) and so the synchronised timing of postoperative analgesia is crucial. Although described as 'one shot' it is not uncommon for the injection needle to need repositioning multiple times during the procedure and PNB may require multiple skin punctures. 'Continuous' PNB, where a catheter is left in place for a longer period for extended post-anaesthesia analgesia, is not considered in the current study.

2.1 PNB Activity

Although institutional PNB activity is routinely documented in hospital databases and regional/national/international PNB activity is summarised in various registries, publicly accessible data on rates of overall procedures is limited.[1] Nevertheless, it is clear that PNB is a very common procedure albeit with potentially significant variation in activity between centres. One study published data from the 19 centres reporting to the International Registry of Regional Anesthesia involving 23,271 PNB procedures performed on 16,725 patients for 18,271 surgical operations between 1st June 2011 and 1st May 2014.[2] Data presented at the American Society of Anesthesiologists annual conference in 2016 revealed 8,229 PNB procedures over a 48 month period (2012 to 2014) at one large US medical centre,[3] whereas another large centre reported approximately 13,000 to 15,000 procedures per year and an internal quality assurance database that had accrued nearly 90,000 PNB procedures between 2009 and 2016.[4] One of the most recent reports of the numbers of PNB procedures undertaken by individual clinicians comes from a survey of 422 Swiss anaesthesiologists.[5] Just under 40% of those who described themselves as 'expert' in the use of PNB (*n*= 63; 15%) reported 11-15 procedures per week, 50% of those who described themselves as 'experienced' (*n*= 209; 50%) reported 6-10 procedures per week, just under 60% of those who described themselves as having 'some experience' (*n*= 119; 28%) reported 6-10 procedures per week, whereas just under 60% of those who described themselves having 'little experience' (*n*= 25; 4%) reported 1-5 procedures per week. Only four (1%) had no experience in the use of PNB.

2.2 Benefits and Risks of PNB

The principal advantages of PNB are effective anaesthesia and immobilisation of the target area(s) for surgery whilst avoiding the side effects of a general anaesthetic. Compared to general anaesthesia in patients undergoing ambulatory hand surgery PNB was associated with a shorter duration of stay in the post-anaesthesia care unit ($p < 0.001$), lower pain ratings in the first two hours following surgery ($p < 0.001$), a greater time to first post-operative analgesic request ($p < 0.001$), reduced opioid consumption during hospital stay ($p < 0.001$), reduced nausea/vomiting ($p < 0.05$) and earlier

discharge ($p < 0.001$).[6] Although generally considered safe PNB is not without complications which are often minor but can be serious and potentially fatal. For instance, there were 3 episodes of cardiac arrest in one prospective survey of 21,278 PNB procedures in France which equates to a rate of 1.4 per 10,000 procedures.[7]

2.3 PNB and Nerve Injury

The complication of PNB that has attracted most attention in the literature is nerve injury. The main mechanisms of PNB mediated damage include mechanical trauma, ischemia, local anaesthetic toxicity, and inflammation. Based on two widely-cited studies,[8,9] patient documentation advising of the risks of PNB published by The Royal College of Anaesthetists in the UK quote an incidence of less than 1 in 10 for temporary nerve damage, with 92% to 97% of patients recovering within four to six weeks and 99% of patients recovering within a year, and an incidence of between 1 in 2,000 and 1 in 5,000 for permanent nerve damage.[10] That most nerve injuries recover within weeks suggests neuropraxic damage (damage to the myelin sheath typically associated with nerve stretching or compression where the axons and endoneurium, perineurium, and epineurium remain intact); the least serious classification of nerve injury that carries the most favourable prognosis.[11,12] In truth, the exact nature of nerve damage following PNB is not clear as estimates vary according to how nerve injury is defined and assessed. As opposed to histological confirmation in animal and cadaveric studies, clinical investigations may include any or all of i) physician examination of sensory and motor deficit; ii) neurophysiological examination (nerve conduction studies and electromyography); and increasingly, iii) nerve imaging techniques (high-resolution ultrasound and magnetic resonance imaging).[13] A further complicating factor is that not all nerve injuries are a direct result of PNB and other factors need to be taken into account.[14] In one case-series involving more than 7,000 PNB procedures nerve injuries were more than nine times more likely to be due to a non-anaesthesia cause than a PNB cause.[9] On the other hand it is possible that the incidence of nerve injury is under-reported as studies that follow-up patients more rigorously report higher incidences of nerve injury following PNB.[15] Litigation claims analysis suggests that most claims following regional anaesthesia are for 'permanent minor' injuries and the total cost of claims related to upper/lower limb blocks exceeded £1m according to National Health Service Litigation Authority data between 1995 and 2007.[16,17] Even if nerve injuries are rare, minor and mostly transient they present a potentially sizeable problem at a healthcare system or population level when the overall number of PNB procedures are taken into account. Moreover, although a hugely under-researched area, patients experiencing more severe and/or longer lasting nerve damage may be more likely to consume greater healthcare resources whilst persistent nerve injury may have negative consequences in terms of patient's physical function, ability to work and quality of life especially considering the adverse impact of general post-surgical neuropathic pain.[18-20]

2.4 Essential Requirements for a PNB Procedure

There are few overarching clinical guidelines for PNB as the steps when undertaking the procedure differ depending upon the type of block, of which there are many. As clinical practice is generally determined by local protocol and individual clinical discretion there is considerable variation in technique amongst anaesthetists performing the same types of PNB procedure. Despite the absence of clinical guidelines, the number and diversity of PNB types and the heterogeneity in clinical practice, an effective and safe PNB may be considered as having two broad essential requirements: i) accurate localisation of the target nerve(s) together with ii) controlled injection of the appropriate amount of LA near to the nerve without the needle touching or entering the nerve structure.

2.4.1 Evidence for Accurate Localisation of the Target Nerve

The modalities of nerve stimulation (NS) and ultrasound guidance (UG) have largely replaced using anatomical landmarks such as bones or arteries to identify the site of needle insertion for PNB. NS involves the use of low-current electrical nerve stimulators, linked to the injection needle, which produce a small twitch of muscles supplied by a nerve when the needle nears the target nerve. UG involves the use of high-resolution real-time ultrasound imaging to visualise the target nerve thus facilitating needle placement adjacent to the nerve. A 2015 Cochrane Review (CR) of upper and lower limb PNB summarised 32 randomised controlled trials in establishing UG/UG+NS/NS as the standard of care for the accurate localisation of target nerves.[21] The CR found that UG produced superior PNB success rates, with more blocks being assessed as sufficient for surgery following sensory or motor testing (Mantel-Haenszel (M-H) odds ratio (OR),fixed-effect 2.94; 95% confidence interval (CI) 2.14 to 4.04), and fewer blocks requiring supplementation or conversion to general anaesthetic (M-H OR, fixed-effect 0.28; 95% CI 0.20 to 0.39) compared with the use of NS or anatomical landmark techniques. As some anaesthetists use UG in combination with NS the CR also compared UG+NS versus NS alone and found similarly favourable effects for UG+NS in terms of adequacy of block (M-H OR, fixed-effect 3.33; 95% CI 2.13 to 5.20) and the need for supplementation or conversion to a general anaesthetic. (M-H OR, fixed-effect 0.34; 95% CI 0.21 to 0.56). Trials included in the CR didn't provide as much detail on complications compared to measures of PNB success although it isn't clear whether complications were rare and so were not detected, or were simply not reported. Meta-analysis was possible for vascular puncture and paraesthesia complications although these comparisons included significantly fewer studies and participants. A lower incidence of paraesthesia was found for UG (M-H OR, fixed-effect 0.42; 95% CI 0.23 to 0.76) although there was a high level of heterogeneity in this analysis due to the large number of events (44.90%) in the NS arm of one study whereas the comparison for UG+NS was not statistically significant (M-H OR, fixed-effect 0.97; 95% CI 0.30 to 3.12). Unusually for a CR the authors didn't define one of the main outcomes assessed - paraesthesia (abnormal sensory symptoms typically characterised as tingling, prickling, burning, or pins and needles) - although this might be due to the fact that some trial assessments of 'paraesthesia' measured abnormal motor function more than abnormal sensory function and it is unclear whether trials measured this outcome intraoperatively/immediately postoperatively or longer-term. Although inadequate reporting limits the inferences that can be drawn, that the rate in the anatomical landmark/transarterial approach arm was only 17 in 100 seems unduly low given these techniques involve eliciting intentional paraesthesia whilst the rates of 6.25 per 100 in both the UG and NS arms hints at possible intraoperative nerve injury even within experimental arms that were otherwise shown to produce favourable outcomes. Although the rate of paraesthesia in the anatomical landmark/transarterial approach arm seems low further evidence against these techniques is that the rate of paraesthesia in the UG+NS arm was 7.32 per 100.

2.4.2 Evidence for Controlled Injection of the Appropriate Amount of Local Anaesthetic Near to the Nerve

In contrast there is no good evidence identifying a standard of care regarding controlled injection of the appropriate amount of local anaesthetic (LA) near to the nerve without the injection needle touching or entering the nerve structure. Historical and most contemporary practice is based upon the concept of 'syringe-feel'; perception of higher than normal resistance to injection which may indicate accidental nerve penetration *i.e.* delivery of LA into the nerve rather than close to the nerve.[22] In summary: in a two operator process the anaesthetist performing the procedure places the needle using UG/UG+NS/NS (or anatomical landmarks *etc*.) as already described. The anaesthetic assistant then depresses the plunger on the syringe to inject LA and uses the resistance felt to judge the amount of pressure to apply. It is through this feedback that the anaesthetist determines whether it is safe to continue. If the assistant reports that the ability to inject is difficult this may indicate that the needle

has accidentally penetrated the nerve. *NB:* Although intraneural (below the epineurium) needle penetration does not invariably lead to functional nerve injury,[23] intentional intraneural injection or any type of needle-to-nerve contact for the purposes of achieving more rapid onset of block is not recommended.[24-26] Whilst the concept of using 'syringe-feel' to detect high injection pressures, which may be a possible indicator of unintentional needle-to-nerve contact, intraneural penetration or intrafasicular (within the perineurium) penetration, is theoretically attractive it is unreliable in practice. The ease of depressing the syringe is subjective and dependant on the assistant's clinical knowledge and experience of performing these procedures. Studies have demonstrated operators vary widely in their perception of appropriate force and rate of injection during PNB. For example, of 30 anesthesiologists in a simulation study who were asked to inject LA as they would in their everyday practice via a standard syringe and needle assembly, 21 (70%) initiated injection using a force that resulted in pressures greater than 20psi; 15 (50%) used a force greater than 25 psi, and 3 (10%) exerted pressures greater than 30 psi. Injection pressure varied as much as 20-fold among needles of the same gauge/length from different manufacturers ($p < .01$).[22] In another blinded experiment of 'syringe-feel' using ovine nerve, muscle, bone and tendon preparations, when asked to identify what tissue they were injecting only 10 (30%) of 33 experienced regional anesthesiologists correctly identified the nerve.[27] Altogether this evidence has led the American Society of Regional Anesthesia and Pain Medicine (ASRA) to conclude 'unfortunately anesthiologists cannot reliable discern injection pressure based upon 'syringe-feel' alone'.[24] More explicitly, the current evidence-based ASRA Practice Advisory states: 'The common practice of subjectively assessing injection pressure by 'hand feel is inadequate'.[24]

Given the limitations of 'syringe-feel' the obvious question is can any other clinical approach minimise the risk of nerve injury when undertaking PNB? Evidence from animal, bench, cadaver and clinical studies has been systematically examined in multiple comprehensive reviews of potential alternative modalities: UG, NS, UG+NS, intentionally induced intraoperative paraesthesia and injection pressure monitoring.[12, 24-26] The conclusions and evidence-based recommendations arising from these reviews are remarkably consistent:

- Whilst UG can detect intraneural needle penetration via visualisation of the needle tip within the nerve, increase in cross-sectional area of the nerve by at least 15%, spread of LA within the epineurium on proximal-to-distal scanning or real-time visualisation of fascicle separation on injection any of these indicate intraneural injection has already occurred. Current UG technology does not have adequate resolution to discern inter/intra fascicular injection and adequate images of the needle-to-nerve interface are not consistently obtained by all operators and in all patients

- Presence of an evoked motor response with NS at a current of less than 0.5 (0.1 ms) indicates intimate needle-nerve relationship, needle-to-nerve contact, or intraneural needle placement although absence of a motor response at a current of up to 1.8 mA does not exclude needle-to-nerve contact, or intraneural needle placement

- Intentional intraneural needle insertion may not necessarily cause nerve injury although it is not recommended as a clinical technique. Intrafascicular injection should be avoided because it can cause histological and/or functional nerve injury. Unintentional paraesthesia on injection should prompt needle repositioning. The occurrence of unintentional intraoperative paraesthesia is not a sensitive sign of needle-to-nerve contact but the absence of intraoperative paraesthesia does not reliably exclude needle-to-nerve contact

- Avoidance of high resistance to injection and high opening pressure (the pressure in the needle-tube-syringe assembly before the LA begins to flow) and/or injection pressure (the pressure required to maintain the flow of LA once an injection is initiated) seems to be a reasonable clinical strategy as opening pressures <15 psi are associated with injection into non-neural tissues although injection pressure monitoring seems to be most valuable as a negative predictor of nerve injury. Pressure monitoring systems cannot reliably detect intraneural and/or intrafascicular injection and needle-to-nerve contact and intrafascicular injection are indistinguishable.

- The concept of 'maximum effective needle-to-nerve distance' *i.e.* placing the needle at a more distant point from the target nerve than is currently practiced remains hypothetical. Achieving an effective block without injecting a significantly increased volume of LA to compensate for the increased distance, which potentially increases the risk of both LA toxicity and nerve injury, is likely to be problematic.

In conclusion there is currently no reliable standard of care regarding controlled injection of the appropriate amount of LA near to the nerve whilst ensuring that the needle does not touch or enter the nerve structure whilst performing PNB. The suggestion that modalities such as UG to 'see' the spread of LA can help improve the safety of PNB injection are not supported in the literature.[12,21,24-26] Anaesthetists therefore cannot rely on UG, NS, 'syringe-feel' or injection pressure monitoring as indicators of unintentional needle-to-nerve contact, intraneural penetration or intrafascicular penetration. Whilst the 'Neanderthal practice of no paraesthesia, no anesthesia' has been discredited evidence to support the contemporary practice of 'syringe-feel' is weak at best.[28] Although the effect of bias introduced by increasingly complex PNB procedures in increasingly older and sicker patients cannot be ruled out the incidence of nerve injury hasn't decreased over time despite the considerable advances in UG/NS technology and practice together with an apparent decrease in 'high-risk' anatomical landmark/transarterial approach PNB procedures where intentional paraesthesia is an integral part of the technique. Therefore, as the evidence-based ASRA Practice Advisory suggests, the safest way of preventing nerve damage might be to limit LA opening and injection pressure to levels that are not associated with nerve damage.[24] More specifically, a method that prevents high LA opening and injection pressures is required rather than an approach that simply detects when nerve injury might already have occurred. In other words, a device that allows LA injection in the presence of low opening and injection pressures (as low pressures are correlated with the absence of nerve injury) but that prevents LA injection in the presence of high opening and injection pressures (a conservative safety measure as high pressures are not correlated with the presence of nerve injury) thus prompting the anaesthetist to reposition the needle away from a presumed nerve structure *before* the injection of any LA.

2.5 The SAFIRA System

SAFIRA (SAFe Injection for Regional Anaesthesia) is a novel single-operator medical device that has European Ntory approval (CE mark) and Section 510(k) FDA clearance along with Australian TGA approval. The SAFIRA system monitors and gives accurate and objective real-time feedback on PNB opening pressure and injection pressure which alerts the anaesthetist to high pressures and provides a stimulus to modify technique to prevent potential nerve injury. Furthermore, unlike passive pressure monitoring systems SAFIRA has a pre-set pressure threshold which activates if opening or injection pressures reach a level of >20psi. Although SAFIRA has been comprehensively examined through the process of Clinical Evaluation, safety and performance have not yet been established in a clinical setting.

2.6 Study Rationale

Unintentional needle-to-nerve contact, intraneural penetration or intrafascicular penetration during PNB may cause nerve injury which, even if minor and transient, presents a sizeable problem when the number of PNB procedures are scaled-up to a healthcare system or population level. Patients experiencing more severe and/or persistent nerve injury may experience significant negative consequences in terms of decreased health status, physical function, ability to work and quality of life. Anaesthetists cannot rely on UG, NS, 'syringe-feel' or injection pressure monitoring as indicators of unintentional needle-to-nerve contact, intraneural penetration or intrafascicular penetration. It is possible that the safest way of preventing nerve damage might be to automatically limit LA opening and injection pressure to levels that are not associated with nerve damage. The SAFIRA system is a medical device that limits LA opening and injection pressures to a level of >20psi. This study will assess the safety and performance of SAFIRA in a 'real-world' clinical setting.

3. OBJECTIVES/RESEARCH QUESTIONS

The study will examine:

- Does the device perform as intended in routine clinical practice?
- Is the device safe to use as per intended use, are the known risks acceptable and do any new risks identified impact the benefit-risk ratio?
- What, if any, is the impact on the clinical workflow of PNB procedures when using SAFIRA compared with standard practice?
- What is the user feedback regarding acceptability of and confidence in SAFIRA for performing PNB procedures?

4. METHODS

4.1 Study Design

This prospective, open, non-controlled, single-arm post-market clinical follow-up investigation will involve 128 PNB procedures undertaken by up to 10 anaesthetists trained in the use of the SAFIRA system (by "trained" we mean have read the Instructions for Use Manual prior to using the SAFIRA system) across one UK hospital site, one site in the USA, and one site in Australia. The UK arm of this study will involve 43 PNB procedures undertaken by 3-6 anaesthetists. Subsequent ethics will be acquired from the USA and Australia arms, where required, from appropriate ethical panels based in the respective countries. The overall aim of this study is to ascertain the safety and performance of SAFIRA in a 'real-world' clinical setting. For the purposes of the study any operation that requires more than one simultaneous PNB (*e.g.* for complex lower limb surgery) will be considered a single PNB procedure. The study will be entirely observational. The investigation will not involve allocation (or withholding) of any aspect of clinical care, will not involve any clinical investigation or treatment additional to standard care and will not include any patient-orientated research instruments (*e.g.* multidimensional pain questionnaires) unless routinely used at the participating site. All patients will undergo treatment according to normal clinical practice *i.e.* as determined by local institutional protocol and/or individual clinician discretion. The principal units of analysis will be PNB procedures undertaken with the SAFIRA system and various procedure-related, patient-related and operator-related variables will be assessed.

In summary, at each participating site study assessors (SA) - trained members of the care team not directly involved in the care of patients within the study - will record the following types of data:

i) Procedural data related to anaesthetists use of the SAFIRA system in patients undergoing any type of elective surgery via any type of PNB involving UG/UG+NS/NS;

ii) Routine clinical data (or clinical data potentially available for collection without impacting on patient care) in patients undergoing SAFIRA PNB procedures; and

iii) Anaesthetists appraisal of the SAFIRA system (this will take place via a recorded 20 minute telephone interview this data will be treated as confidential and securely stored at all times).

The study will not consider outcome measures of any of the surgeries undertaken using PNB nor will it consider the underlying effectiveness of UG, UG+NS or NS.

4.2 Device Description

The SAFIRA system is intended for use by trained anaesthetists to administer LA below a specified pressure threshold to a target nerve or nerve bundle in order to achieve PNB. The SAFIRA system does not change clinical practice *per se* as anaesthetists continue to follow normal clinical practice but instead aims to standardise controlled injection of the appropriate amount of LA near to the nerve without the needle touching or entering the nerve structure. Unlike the practice of 'syringe-feel' SAFIRA is a single-operator system comprising a regional anaesthesia needle connected via a catheter to a syringe. The syringe is placed inside the SAFIRA motor housing and via a foot pedal mechanism allows the anaesthetist full control to both aspirate and inject LA at a controlled maximum rate of 0.5ml/sec. The key clinical benefit of the SAFIRA system is that it limits the pressure at which LA can be delivered to 20psi hence avoiding potential damage to the nerve through unintentional needle-to-nerve contact, intraneural penetration or intrafascicular penetration. The SAFIRA Instructions for Use are contained in **Appendix 1**.

Once agreements to participation in the study are in place the Sponsor will provide, without charge, SAFIRA devices to each participating site for exclusive use within this prospective, open, non-controlled, single-arm post-market clinical follow-up investigation. The initial number of devices supplied to the centre will be based on historical PNB activity. The SAFIRA devices will only be used for the investigation and in accordance with the study protocol and Instructions for Use. The hospital site will be responsible for the appropriate storage of the devices and will maintain records documenting the receipt, use, return or disposal of SAFIRA devices supplied for the purposes of the investigation.

4.3 Study Timescale and Study Phases

T From the start of site setup to publication of the final report the study will take a total of 18 weeks. An overview of the phases of the investigation is shown in **Figure 1**.

4.4 Study Populations

4.4.1 Sites & Site Study Assessors

The UK arm of this investigation will take place at one UK hospital site (Queen Elizabeth Hospital King's Lynn Foundation Trust) that offers UG/UG+NS/NS PNB regional anaesthesia for surgical procedures. Queen Elizabeth Hospital King's Lynn Foundation Trust and a Chief Investigator from this site will be appointed by the Sponsor. As a pragmatic real world investigation there will be no absolute site-related inclusion/exclusion criteria. The Queen Elizabeth Hospital King's Lynn Foundation Trust, and

other centres involved in the study, will be required to provide signed agreement to participation in the study including use of the SAFIRA system in consecutive patients scheduled to undergo elective surgery via UG/UG+NS/NS PNB (unless there are clinical reasons for not using SAFIRA) and who can identify a suitable SA for data collection. Each site will be considered initiated once all arrangements for conduct of the investigation at that site are confirmed against a site initiation checklist.

The SA will be a member of the care team (*e.g.* nurse, junior medical staff) who, in order to guarantee data collection, will not be directly involved in the care of patients within the study. The SA will not need to be blinded to care as the investigation is a single-arm observational study. Sites involving multiple participating anaesthetists will have more than one SA. The SA at each site will be trained in data collection during site initiation and the hospital site will not be initiated until SA training has been completed. All time that a SA spends working on the study will be remunerated by the Funder/Sponsor.

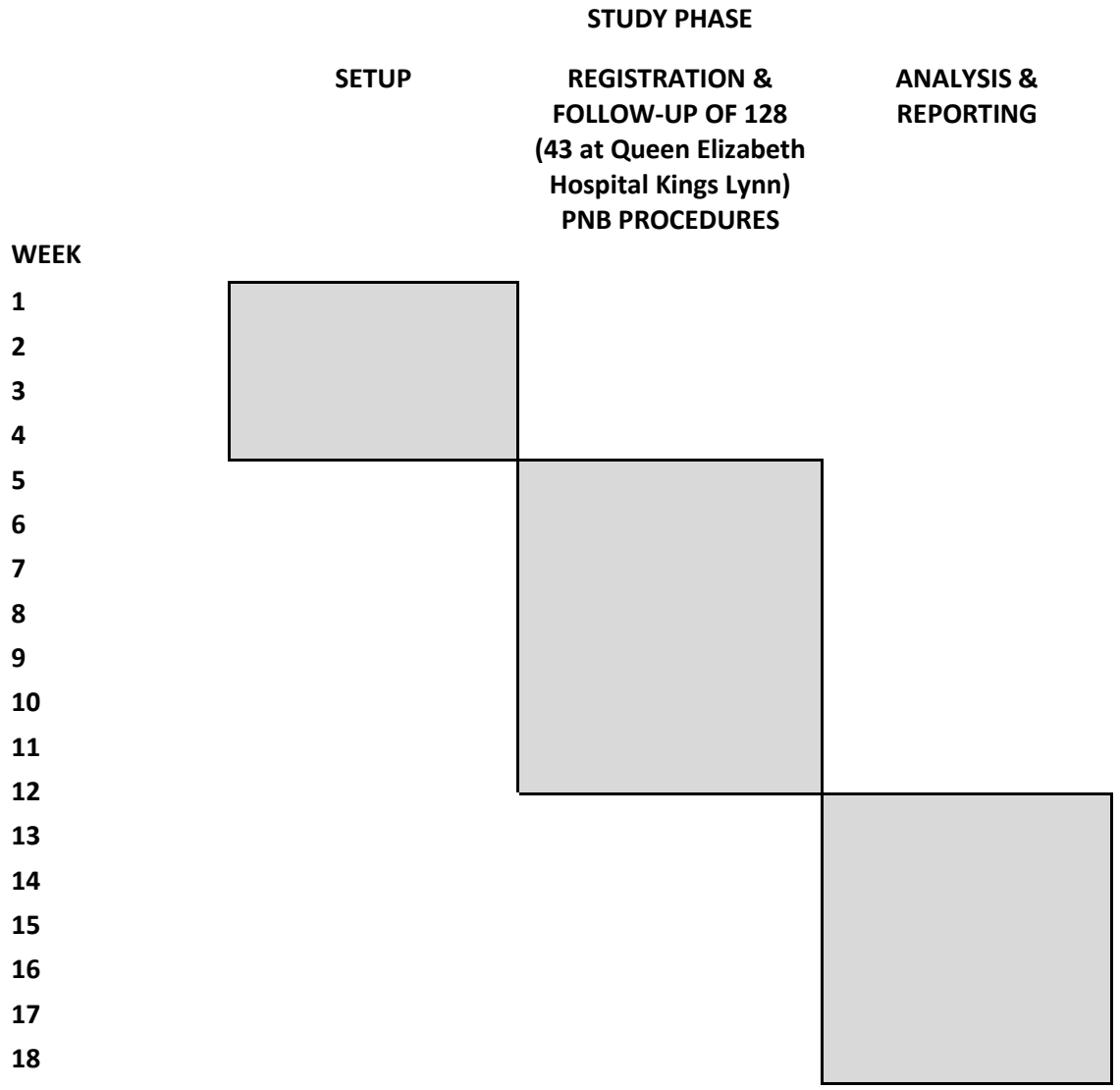

Figure 1: Study Timescale and Phases

4.4.2 Participating Anaesthetists

Anaesthetists at Queen Elizabeth Hospital King's Lynn Foundation Trust and each institution signing up to the studywho have at least 6-months clinical experience of performing UG, NS or UG+NS PNB will be invited to take part in the investigation. Before commencement of this study and to mitigate against 'initial effect' there will be a small running cohort for learning of up to 50 patients. Anaesthetists who only perform PNB using anatomical landmark or transarterial approach will not be invited to take part as these techniques typically require elicitation of intentional paraesthesia to confirm needle placement and the superiority of UG/UG+NS/NS over these methods has been definitively established through systematic review and meta-analysis. Based on the data considered above the intention is to recruit at least two anaesthetists who undertake ≤5 PNB procedures per week and at least two anaesthetists who undertake ≥20 PNB procedures per week. Those anaesthetists expressing an interest and who agree to the study protocol including use of the SAFIRA system in consecutive cases (unless there are clinical reasons for not doing so) will undergo training in the use of SAFIRA during site initiation by representatives of the Sponsor who, other than being available in the case of queries regarding routine use of the device, will have no other role in the study. Importantly, whilst clinical participants in the study will be compensated for their time, no individual participant in the study will either have a stake in the company or stand to gain by producing favourable results. It will be made clear that other than using SAFIRA in place of 'syringe-feel' anaesthetists will follow normal clinical practice. However, anaesthetists will not be able to use any medical device designed to objectively monitor injection pressure (*e.g.* B. Braun Medical Limited BSmart™ Injection Pressure Monitor, Pajunk Medical Systems NerveGuard Automatic Injection Pressure Limiter), any alternative method to monitor/limit injection pressure (*e.g.* Compressed Air Injection Technique, Improvised Pressure Gauge) or any custom-made device which would potentially conflict with use of the SAFIRA system. The investigation will only involve anaesthetists who have successfully completed SAFIRA training and who provide signed agreement to participation in the study. To permit comparisons with published data from PNB databases, surveys and registries the following background information on participating anaesthetists experience and practice will be collected:

- Current clinical grade
- Number of years working in anaesthesia
- Number of PNB performed per week
- Number of different PNB techniques performed (choice from list of most common PNB procedures)
- Primary technique of nerve localisation (UG alone, NS alone, UG + NS)
- Using any Injection pressure monitoring (Y/N)
- Estimated experience in PNB (expert, experienced, some experience, little experience)

4.4.3 PNB Procedures

As the study is a prospective, open, non-controlled, single-arm post-market clinical follow-up investigation in a real-world clinical setting there will be minimal inclusion and exclusion criteria as the objective is to assess safety and performance in 'all-comer' PNB procedures undertaken with the SAFIRA system.

4.4.3.1 Inclusion Criteria

PNB procedures involving patients aged > 18 years referred for any type of elective surgery suitable for PNB and who are offered and agree to surgery that will be performed via any UG, any UG+NS and any NS single-injection PNB regional anaesthesia. Any type of PNB will be included in the study.

4.4.3.2 Exclusion Criteria

- PNB procedures involving patients aged < 18 years
- PNB procedures involving (pre-scheduled) continuous PNB
- PNB procedures involving patients undergoing emergency surgery
- PNB procedures involving patients with absolute contraindications to PNB *NB*: patients who have a history or evidence of pre-existing neurologic deficit, coagulopathy, opioid or LA allergy/intolerance, systemic infection or infection at the site of the intended PNB at pre-operative assessment but who are otherwise offered and agree to PNB will be included in the study although the presence any major risk factors will be recorded
- PNB procedures involving any medical device designed to objectively monitor injection pressure (*e.g.* B. Braun Medical Limited BSmart™ Injection Pressure Monitor, Pajunk Medical Systems NerveGuard Automatic Injection Pressure Limiter), any alternative method to monitor/limit injection pressure (*e.g.* Compressed Air Injection Technique, Improvised Pressure Gauge) or any custom-made device which would potentially conflict with use of the SAFIRA system.

4.5 Registration and Follow-Up of PNB Procedures

The study is designed around the prospective consecutive registration of 128 PNB procedures (43 at the Queen Elizabeth Hospital King's Lynn) between theparticipating centre where the SAFIRA system will be used instead of the 'syringe-feel' method. In order to allow the SA at each site to plan data collection on a day-to-day basis PNB procedures scheduled will be evaluated on the day of surgery. Standard practice is that patients referred for elective surgery are assessed by the anaesthetist at least one day prior to scheduled surgery and, after discussion of risks and benefits, patients are offered a choice of anaesthetic based on clinical assessment by the anaesthetist. *NB*: Patient consent to anaesthetic may be obtained independently of patient consent to surgery although consent for anaesthesia has traditionally been considered as implied once the patient consents to surgery with the surgical consent stating that anaesthesia will be needed for the surgery and that there are associated risks with anaesthesia. Participating anaesthetists assessing patients at least one day prior to surgery will notify the SA of any patient aged > 18 years who has been offered and who has agreed to surgery where the anaesthetist intends PNB anaesthesia and perceives no clinical reason for not using SAFIRA. The assumption will be that the SAFIRA system will be used in all of these patients. However, records will be kept for those who: i) didn't proceed to surgery; ii) proceeded to surgery but who didn't undergo PNB with SAFIRA; and, iii) weren't considered suitable for SAFIRA when assessed by the anaesthetist on the day prior to surgery.

The registration and follow-up of the 128 PNB procedures (43 at the Queen Elizabeth Hospital Kings Lynn) is schematically outlined in **Figure 2**. For ease of illustration registration and follow-up is shown across a seven day week although in practice is it anticipated most activity will occur over a five day week. It is also assumed that recruitment may not be equal across participating sites and/or participating anaesthetists. As a relatively low estimate of per anaesthetist PNB activity has been used to estimate accrual of 43 PNB procedures is possible that registration and follow up will be achieved in a shorter time than shown.

The SA at each site will notify the Chief Investigator and Sponsor of the registration and follow-up of each PNB procedure so that progress towards the total sample size of 128 PNB procedures can be monitored. Registration of procedures will stop when the 128th PNB procedure has been registered and surgery has taken place. Any PNB procedures registered at this point which proceed to surgery the day after will be included in the study. Any PNB procedures registered at this point which do not proceed to surgery the day after will not be included in the study.

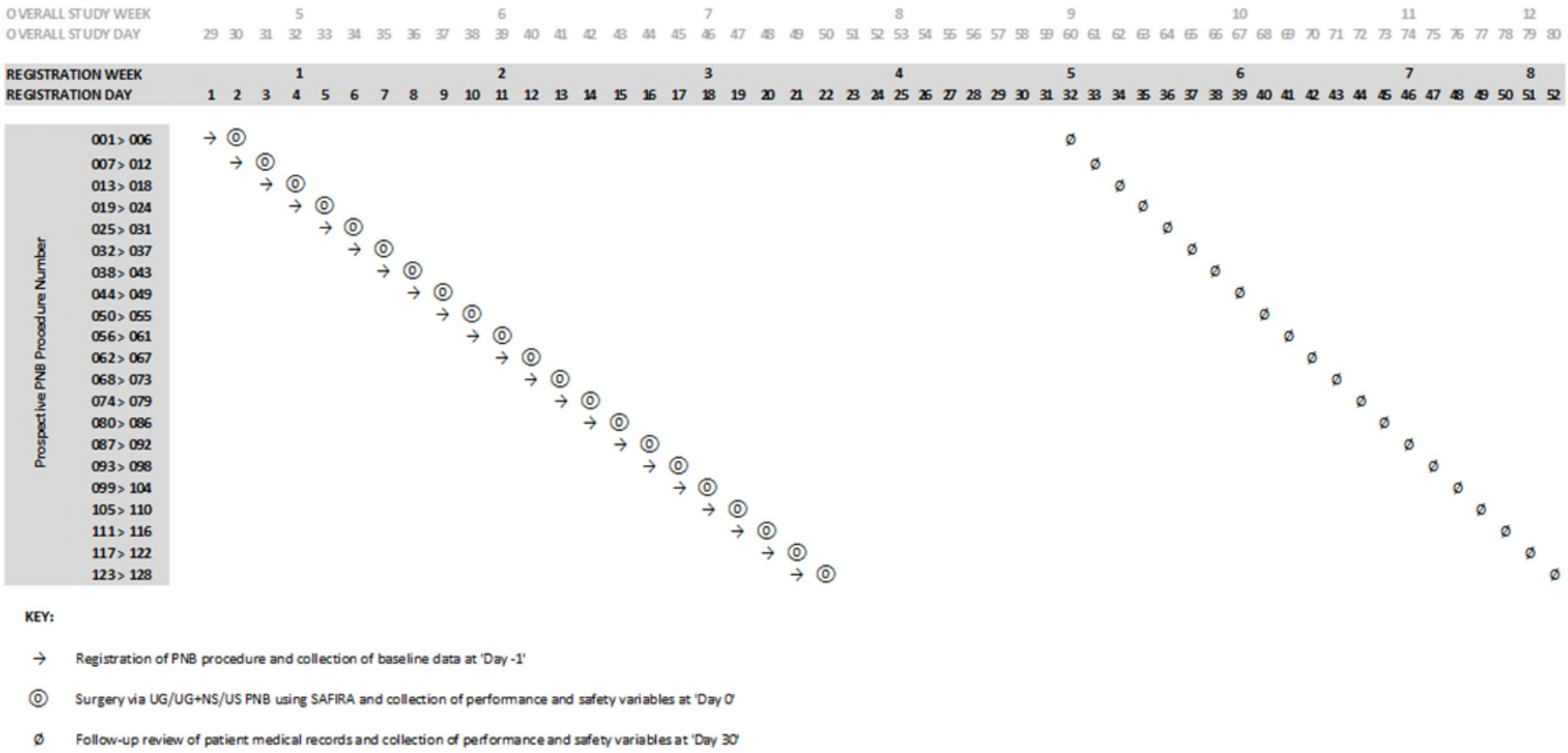

Figure 2: Study PNB Registration and Follow-Up Schedule

Each PNB procedure will be included in the study for a total of 32 days.

- The SA will register each PNB procedure notified to them by the anaesthetist on the day prior to surgery ('Day -1' for that PNB procedure).
- Surgery via UG/UG+NS/NS PNB using the SAFIRA system in place of the 'syringe-feel' method will take place the day after study registration ('Day 0' for that PNB procedure)
- Review of patient medical records will take place 30 days after surgery ('Day 30' for that PNB procedure)

Based on the activity data cited in the background a conservative estimate is 4 PNB procedures per participating anaesthetist per week. With 3 participating anaesthetists a total of 12 PNB procedures will be registered in a week. Therefore, registration of a total of 128 PNB procedures and follow up to 30 days after surgery will take a maximum of 52 days.

- Registration of all 128 PNB procedures at 'Day -1' will take a total of 21 days (Registration/Follow-Up Day 1 to Day 21)
- Completion of all 128 PNB procedures with SAFIRA at 'Day 0' will take a total of 21 days (Registration/Follow-Up Day 2 to Day 22)
- Review of patient medical records for all 128 PNB procedures at 'Day 30' will take a total of 21 days (Registration/Follow-Up Day 32 to Day 52)

Cancellation of operations when a PNB procedure has already been registered for the study is inevitable. If a cancelled operation is rescheduled whilst accrual of the 128 PNB procedures is still ongoing the rescheduled surgery will be included in the study. If an operation is not rescheduled or is rescheduled after 128 PNB procedures have already been registered the PNB procedure will not be included in the study. Minimal loss to follow up is anticipated as the study does not involve any clinical or research investigations additional to normal care. Review of patient medical notes at 'Day 30' will be possible even if a patient is deceased or otherwise unavailable for follow-up.

4.6 Anaesthetic & Surgical Procedures

The study will be entirely observational and there will be no experimental intervention. As a European and Australian regulatory approved andUS FDA cleared device, the SAFIRA system is already available to clinicians who wish to use it in routine clinical practice. Other than using SAFIRA in place of the 'syringe-feel' method in 128 consecutive UG/UG+NS/NS PNB procedures (unless there are clinical reasons for not using SAFIRA) anaesthetists, trained in use of the SAFIRA system (by "trained" we mean have read the Instructions for Use Manual prior to using the SAFIRA system), will follow normal clinical practice (*i.e.* as determined by institutional protocol and/or individual clinician discretion including local variations in practice such as whether or not to routinely prescribe midazolam for anxiety) but without the need for an assistant† and with one minor modification: *i.e.* instead of manually depressing the syringe to inject LA using 'syringe-feel' (which is described in the ASRA Practice Advisory as 'inadequate') the SAFIRA system will employed according to the Instructions for Use. The study places no restrictions on type of UG or NS equipment used nor the UG/UG+NS/NS technique.

† An assistant will be on standby should SAFIRA need to be converted to manual operation in the case of equipment failure (the SAFIRA syringe can be disengaged from the driver assembly in order for a second operator to depress the plunger manually).

4.7 Study Variables and Schedule of Assessment

VARIABLE	'DAY -1' BASELINE	'DAY 0' INTRA-OPERATIVE	'DAY 30' FOLLOW-UP
Age	•		
Sex	•		
Weight	•		
Height	•		
ASA physical status	•		
Pre-existing neurological deficit	•		
Coagulopathy	•		
Known opioid/LA allergy/intolerance	•		
Evidence of systemic infection	•		
Evidence of infection at PNB site	•		
Previous PNB block in area to be blocked	•		
History of LA toxicity	•		
Time to perform block		•	
Block success		•	
Adequate block		•	
Supplementation/conversion		•	
Evidence of potential acute nerve injury		•	
Patient-reported symptoms		•	
Anaesthetist-reported events		•	
Evidence of persistent nerve injury			•
No. Needle punctures		•	
No. Needle redirects		•	
Block onset time		•	
Event-free SAFIRA assembly/deployment		•	
SAFIRA malfunction/failure		•	
Major clinical complications		•	
Minor clinical complications		•	
LA volume required		•	
Anaesthetist appraisal of the SAFIRA system		•	
Infection at PNB site			•
Falls			•
PNB limb trauma			•
Postoperative 1hr pain score			•
Postoperative 24hr analgesic consumption			•
Length of hospital stay			•
Anaesthetist appraisal of the SAFIRA system			•
Operative details		•	

Table 1: Study Variables and Schedule of Assessment

(For definitions see main text)

Study variables and the schedule of assessment are listed in **Table 1**. Variables have been carefully selected to allow comprehensive assessment of safety and performance via an observational study design whilst allowing comparisons with the main outcomes reported in the literature, specifically, those of the CR examining upper and lower limb PNB. Attempts have also been made to distinguish evidence of intraoperative nerve injury (symptoms of 'paraesthesia' or suspected/reported unintentional needle-to-nerve contact or intraneural/intrafasicular penetration) from evidence of persistent nerve injury in the 30 days following surgery.

In summary: each SA will create a new registration on the study database for each PNB procedure notified to them by the anaesthetist on the day prior to surgery (*i.e.* 'Day -1') using a secure electronic case report form (eCRF). Registration will involve an identification number unique to that PNB procedure so as to prevent duplication errors and the eCRF will contain no individual patient identifiable information. Baseline variables will be recorded on the eCRF on Day -1. The SA will directly observe each SAFIRA PNB procedure on 'Day 0'. Intraoperative procedure-related, patient-related and operator-related variables will be recorded on the eCRF. The SA will review medical records 30 days following surgery ('Day 30') and any evidence of persistent nerve injury will be recorded on the eCRF. For rescheduled PNB procedures 'Day 0' will not be the day after registration and so 'Day 0' and 'Day 30' assessments will be shifted accordingly.

4.7.1 Patient Baseline Variables

- Age
- Sex
- Weight
- Height
- American Society of Anesthesiologists (ASA) physical status classification
- Pre-existing neurological deficit (Y/N)
- Coagulopathy (Y/N)
- Known opioid/LA allergy/intolerance (Y/N)
- Evidence of systemic infection (Y/N)
- Evidence of infection at PNB site (Y/N)
- Previous PNB Block in area to be blocked (Y/N)
- History of local anaesthetic toxicity (Y/N)

4.7.2 Primary Variables

The primary procedure performance variable at 'Day 0' will be time to perform block. This will be defined as time from the first application of the probe on skin for UG or first application of needle on the skin for NS (or whichever occurs first if UG+NS is used) to final removal of the PNB LA needle.

The primary clinical performance variable at 'Day 0' will be a composite measure of block success. This will be defined as adequate block (sufficient blocking of the transmission of nerve impulses as assessed by routine institutional sensory and/or motor testing protocol to allow surgery to proceed) AND no

block conversion (avoidance of rescue block, ,) *NB*: both composite and separate measures of block success will be reported.

The primary safety variable at 'Day 0' will be will be a composite measure of evidence of potential acute nerve injury. This will be defined as any patient-reported severe and painful symptoms such as tingling, prickling, burning, uncomfortable pins and needles or any type of electric shock sensation during the PNB procedure AND suspected or confirmed needle-nerve contact, intraneural needle penetration or intrafascicular needle penetration as reported by the anaesthetist *NB*: both composite and separate measures of potential nerve injury will be reported.

The primary safety variable at 'Day 30' will be evidence of persistent nerve injury. This will be defined as any documented evidence in the patient medical records of sensory and/or motor deficit including: i) patient-reported chronic, severe and painful symptoms such as tingling, prickling, burning, uncomfortable pins and needles or any type of electric shock sensation; ii) patient-reported limb or muscle weakness or iii) clinician-observed sensory and/or motor deficit lasting longer than 48 hours after surgery. Sensory and/or motor deficit in a different regional area to that of the PNB will be recorded but will be considered separately to sensory and/or motor deficit in the regional area of the PNB.

4.7.3 Secondary Variables ('Day 0')

- No. Needle punctures (any new needle insertion through skin)
- No. Needle redirects (any needle insertion-withdrawal-insertion of ≥10mm)
- Block onset time (interval between completion of LA injection and adequate sensory block to permit surgery in distribution of blocked nerve)
- Event-free SAFIRA assembly/deployment (any suspected or reported issue in any of the steps of the SAFIRA Instruction for Use)
- SAFIRA malfunction/failure (any event requiring conversion to manual injection)
- Major complications (cardiac arrest, pneumothorax, death, other (specify))
- Minor complications (vascular puncture, haematoma, local anaesthetic toxicity, cardiac arrhythmia, systemic hypotension, other (specify))
- LA volume required
- Anaesthetists appraisal of the SAFIRA system after completing each PNB procedure
    - *Injection Pressure (How important is limiting LA opening/injection pressure in your own clinical practice: Not at all important/Quite unimportant/Neither unimportant or important/Quite important/Very important)*
    - *Ease of Use (Compared to usual practice SAFIRA is easy to use: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*
    - *Effectiveness (Compared to usual practice SAFIRA is effective: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*
    - *Drawbacks (Compared to usual practice SAFIRA has few drawbacks: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*

- *Workload (Compared to usual practice SAFIRA increases workload: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*
- *Preference (Compared to usual practice I prefer SAFIRA: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*

4.7.4 Secondary Variables ('Day 30')

- Infection at PNB site
- Falls (any documented inpatient or at home falls in 30 days following surgery)
- PNB limb trauma (any documented inpatient or at home trauma (scalds, burns, severe pressure sore) in 30 days following surgery)
- Postoperative 1hr pain score (assessed using standard institutional method)
- Postoperative 24hr analgesic consumption
- Length of hospital stay
- Anaesthetists appraisal of the SAFIRA system after completing all PNB procedures
  - *Injection Pressure (How important is limiting LA opening/injection pressure in your own clinical practice: Not at all important/Quite unimportant/Neither unimportant or important/Quite important/Very important)*
  - *Ease of Use (Compared to usual practice SAFIRA is easy to use: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*
  - *Effectiveness (Compared to usual practice SAFIRA is effective: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*
  - *Drawbacks (Compared to usual practice SAFIRA has few drawbacks: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*
  - *Workload (Compared to usual practice SAFIRA increases workload: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*
  - *Preference (Compared to usual practice I prefer SAFIRA: Strongly disagree/Disagree/Neither disagree or agree/Agree/Strongly agree)*

4.7.5 Operative Details ('Day 0')

- Type of surgery, type of PNB(s), type of needle, type of LA, UG/NS equipment and details of techniques used, premed, intraoperative and post-operative analgesic regimens

4.8 Adverse Event (AE)/Adverse Device Effect (ADE), Serious Adverse Event (SAE)/Serious Adverse Device Effect (SADE) and Device Deficiencies (DD)

The conclusion of Clinical Evaluation and Risk Management of the SAFIRA system is that there are no unacceptable risks of harm to the patient or to the user of the device when used under normal conditions and for its intended use. There are no Adverse Device Effects (ADE) or Serious Adverse Device Effects (SADE) anticipated from use of the SAFIRA system when it is used, as intended, by trained anaesthetists to administer LA below a specified pressure threshold to a target nerve bundle in order to achieve PNB. However, any Adverse Event (AE)/ADE, Serious Adverse Event (SAE)/ SADE or

Device Deficiency (DD) arising the conduct of the study will be recorded. SAE/SADE and DD that might have led to a SADE will be reported to the Sponsor, whether or not they are considered causally related to the SAFIRA system, as soon as possible and in all cases within 24 hours of the event. All such events will be jointly reviewed by the Chief Investigator and Sponsor to determine causality in respect of the SAFIRA medical device. In circumstances when the Chief Investigator and Sponsor agree that the device poses an unacceptable risk the study will be stopped immediately. In all circumstances participating anaesthetists and site medical teams are responsible for ensuring that procedures are in place to deal with any medical emergencies arising during PNB procedures irrespective of whether or not they are considered causally related to the SAFIRA system. AE/ADE/SAE/SADE/DD are defined in **Appendix 2**.

4.8 Statistical Considerations

4.8.1 Sample Size

The original intention was to conduct a cohort study comparing the SAFRIA system with a historical control of UG/UG+NS/NS PNB data extracted from registries and the CR of upper & lower-limb PNB that would have been powered for non-inferiority testing of key safety and performance outcomes with a pre-defined non-inferiority margin after propensity score matching of key baseline variables to account for potential differences in the sample populations. Databases/registries documenting PNB practice and the experimental trials summarised in the CR are valuable and potentially complementary resources as observational and randomised controlled trial data offer differing methodological advantages/disadvantages. However, it was established that the limited public accessibility of registry data together with the low prospect of obtaining individual patient level data on which to match baseline variables would not have allowed this.

Sample size calculation was therefore based on reference values established in the CR examining upper & lower limb PNB. To ensure the study was adequately powered for all primary comparisons the largest sample size computed from all primary variable sample size estimations was used as the sample size for the study. This was for the CR reference value of adequate block. All sample size calculations were undertaken using the TrialSize package (Zhang E, Wu VQ, Chow SC, Zhang HG (2013). TrialSize. R package v.1.3) in R software (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Overall, 967 of the 1060 patients (91.2%) randomised to UG or UG + NS within the CR experienced adequate block *i.e*: 649 of the 709 patients (91.5%) randomised to UG experienced adequate block and 318 of the 351 patients (90.6%) randomised to UG + NS experienced adequate block. Assuming at least 91.2% of patients will experience adequate block when PNB is undertaken with the SAFIRA system, a one-sample proportion test[29] for non-inferiority (or one-sample mean test[29] for non-inferiority for continuous variables) with a one-sided Type I error of 0.025, statistical power (1-ß) of 80%, and a 'clinically acceptable' non-inferiority margin of 7% indicated a maximum sample size of 128 PNB procedures would be required to establish non-inferiority assuming no loss to follow-up.

4.8.2 Statistical Analyses

All statistical analyses will be performed using R or equivalent statistical software. All PNB procedures registered for the study will be considered in the statistical analyses including per-protocol procedures (*i.e.* PNB procedures scheduled and carried out using the SAFIRA system) and protocol-deviation procedures (*i.e.* PNB procedures registered for the study and scheduled to be carried out using the SAFIRA system but where SAFIRA ended up not being used) in a form of intention-to-treat analyses.

Summary statistics will be calculated and presented as relative frequencies (proportion, total and 95% CI) for binomial and multinomial categorical data and mean (standard deviation) for parametric continuous data and median (interquartile range) for non-parametric continuous data.

For each primary variable the difference (*D*) and the 95% CI for *D* will be calculated by subtracting the observed proportion of patients within the study from the appropriate reference value established in the CR. For example, $D_{\text{Adequate Block}}$ and the 95% CI for $D_{\text{Adequate Block}}$ will be calculated for the observed proportion of patients experiencing adequate block with the SAFIRA system from the reference value of 91.2% established in the CR. It will be concluded that the SAFIRA system is not inferior to 'syringe-feel' in terms of adequate block if the lower 95% CI bound of $D_{\text{Adequate Block}}$ lies above the lower non-inferiority margin of -7%. Although the study is not designed to determine statistical superiority any 95% CI that lies entirely above zero (no difference) will be taken as evidence of the statistically significant superiority of the SAFIRA system over 'syringe-feel'. Where the primary outcome is a failure rate (*i.e.* a lower value is better), it will be concluded that the SAFIRA system is not inferior to 'syringe-feel' if the upper 95% CI bound of *D* lies below the upper non-inferiority margin of 7%. Any failure rate 95% CI that lies entirely below zero will be taken as evidence of the statistically significant superiority of the SAFIRA system over 'syringe-feel'. For all other outcomes descriptive data will be informally compared against summary statistics reported in the PNB literature. Where possible summary statistics will be stratified according to subgroups *e.g.* type of surgery and UG, NS or UG+NS PNB.

4.9 Data Management

The SA(s) in each centre will collect data through a combination of observation/measurement and the extraction of data from medical records source documentation. The eCRF will be used to record all procedure-related, patient-related and operator-related variables assessed in the study. The eCRF will be only be accessible by trained SAs at each site and will be protected by password. The eCRF for each PNB procedure will be populated on a continuous basis by the SA from the point of registration of an eligible PNB procedure on the day prior to surgery and 'Day -1' baseline variables measurement through intraoperative data collection on 'Day 0' to follow-up of patient medical records at 30-days following surgery on 'Day 30'. No other personnel will be permitted to enter data on the eCRF. Any data that was not available to the SA will be coded as missing with a record of why it is absent. The eCRF will not involve copies of source documentation and will not contain information that will permit the identification of individual patients. TheSA will be responsible for accurate and complete data management and for maintaining the integrity of the eCRF. On completion of 'Day 30' assessment for the final registered PNB procedure will check for accuracy and completeness. The eCRF shall be considered complete when all scheduled data has been entered. Once this has been established the eCRF will be locked. A fully anonymised and un-linked version of the database (*i.e.* containing no identifiable or traceable patient data) will be sent to the Sponsor for data analysis within 5 days of database lock. Each site will be requested to maintain a copy of the eCRF for at least five years. Due to the short timescale of the investigation and the observational design no audit or monitoring by the Sponsor is built into the study schedule. However, the Sponsor retains the right to request SA review of data recorded on the eCRF against source documentation (where this is available) in the case of queries or disputes.

4.10 Study Amendments and Protocol Deviations

Any change to the study design or protocol will require the joint agreement of the Sponsor and Chief Investigator and any amendments will be communicated to all participating anaesthetists. Accidental protocol deviations will be reported to the Sponsor and Chief Investigator. Intentional protocol

deviations will be only be permissible in exceptional circumstances and will require advance approval from the Sponsor and Chief Investigator

4.11 Data Analysis, Interpretation, Reporting and Dissemination

The study Sponsor will have overall responsibility for data analysis, interpretation, reporting and dissemination although this may be delegated to the Chief Investigator. If this responsibility is delegated the Chief Investigator will keep the Sponsor informed of progress and will provide a final report to the Sponsor within an agreed timescale. The Chief Investigator may present the study at conferences and scientific meetings and publish the data in peer-reviewed journals although the Sponsor will be notified in advance. Participating anaesthetists will retain ownership of data related to their own PNB procedures within the study and will be free to present and publish this data. However, participating anaesthetists will need the permission of the Sponsor and Chief Investigator to present or publish overall data.

5. REGULATORY CONSIDERATIONS

Although not a clinical investigation of an investigational device, nor a MHRA regulated clinical trial, the study will be conducted in accordance with the principles of Good Clinical Practice (GCP) and Human Subject Protection (HSP). As the investigation is a wholly observational post-market clinical follow-up study it will be IRB exempt. However, the IRB at the participating site will be notified that the study is taking place. Patient consent will not be sought although anaesthetists assessing patients on the day prior to surgery will inform patients that an audit of a piece of equipment used to perform PNB is taking place although the data will not involve any identifiable patient information. Patients raising any objection will not undergo PNB with SAFIRA and not data will be collected.

To further clarify: the study involves an FDA approved medical device that will be used unmodified and within its intended purpose; the assignment of any patient involved in the study to a particular therapeutic strategy or diagnostic procedure will not be decided in advance by a protocol and will fall within current clinical practice; the decision to use the device will be clearly separated from the decision to include any patient in the study; no diagnostic or monitoring procedures will be applied to patients included in the study, other than those which are ordinarily applied in the course of current clinical practice; epidemiological methods will be used for the analysis of the data arising from the study and the study will not involve the processing of patient confidential information outside of the care team.

5.1 The SAFIRA System Post-market Surveillance Plan

The outcomes of the study will contribute to periodic safety update reports and vigilance reporting within the overall post-market surveillance plan for the SAFIRA system and will help inform any requirement for preventative or field safety corrective action.

5.2 Sponsor and Funder

The study Sponsor and study funder will be Medovate Ltd, The Workplace, Camboro Business Park, Girton, Cambridge, CB3 0QH, United Kingdom. The appointed Medovate representative for the study will be Stuart Thompson.

6. STUDY FINANCE

Agreed with Trust under Clinical Investigation Agreement.

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8. APPENDICES

8.1 SAFIRA Instructions for Use

Definition:

SAFIRA consists of a Sterile Syringe (20ml), Driver and Foot Pedal.
The Sterile Syringe may be manually engaged and disengaged to the gearing of the Driver unit.
The battery operated Driver is activated by means of a cable connected Foot Pedal.
Flowrates are limited by design to a maximum of 0.5ml/sec. Approved needle types and extension tubing may be attached to the luer fitting at the end of the SAFIRA syringe. SAFIRA is to only be used in conjunction with the single use Sterile Syringe. SAFIRAs internal battery power will perform 200 procedures.

Indications for Use:

The Medovate SAFIRA system is intended for use by trained clinicians to administer local anaesthetics below a specified pressure threshold to a target nerve bundle for regional anaesthesia.

Approved Needle Types:

Anaesthesia needles, which fall into the following ranges, have been approved for use with the SAFIRA system:

- The minimum sized needle gauge approved for use with this system is 22G
- The maximum length of the needle approved for use with this system is 120mm

Contraindications:

SAFIRA is not intended for the following use:

- Intravascular delivery
- Delivery of blood, blood products, lipids, fat emulsions or Total Parenteral Nutrition (TPN)
- Infusion of fluids that will enter or contact circulatory blood or cerebrospinal fluid
- Delivery of life-supporting medications where under- or over-delivery may cause serious injury or death

Warnings:

1. Sterile technique should be used at all times during syringe filling, needle introduction and connection. Aseptic technique should be used for removal.
2. Medications or fluids must be administered per instructions provided by the drug manufacturer. Physician is responsible for prescribing drug based on each patient's clinical status (such as age, body weight, disease state of patient, concomitant medications, etc.)
3. Make sure the medication being infused is approved for Regional Anaesthesia / PNB's (e.g. Lidocaine); follow all labelling instructions for medication use.
4. SAFIRA is MRI Unsafe

Warnings (continued)

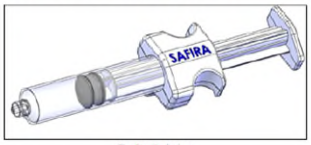
5. Opening injection pressure varies among different tissues, being the highest when the needle tip is lodged in low compliance tissue (e.g., roots of brachial plexus, tendon) and lowest when injected in the soft connective tissues (e.g., adipose tissues, perineural space). SAFIRA limits the injection pressure to less than 20psi.
6. The SAFIRA Syringe is designed for single use in one patient and must not be re-sterilised, reconditioned or re-used. Re-use of the SAFIRA Syringe risks infection (due to accumulation of pathogens in the device that are subsequently injected) or potentially hazardous drug effects (due to residual drug compounds contaminating the intended drug and then being injected).
7. No modification of this equipment is allowed

Precautions:
FEDERAL LAW (USA) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN

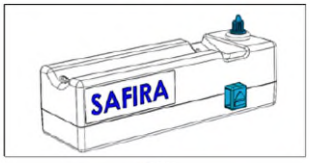
1. SAFIRA has no user serviceable parts. Do not attempt to repair or alter the device.
2. The Sterile Syringe component is disposable and must be discarded after use in accordance with hospital, administrative and /or local government policy.
3. Do not use the Sterile Syringe if the packaging is open or damaged or if the sterile barrier is compromised.
4. The Sterile Syringe component is single use only.
5. The Driver component is a limited reuse device.
6. Flow rates may vary due to fill volume, viscosity and/or drug concentration, positioning the driver above or below the injection site, and temperature.
7. Start delivery within 8 hours of filling the Sterile Syringe. Storage of a filled Sterile Syringe component for more than 8 hours may result in slower flowrates.
8. SAFIRA is not made with natural rubber latex
9. SAFIRA is only to be operated by a trained Health Care Professional.
10. The Sterile Syringe is not intended for measurement use.

SAFIRA Instructions For Use:

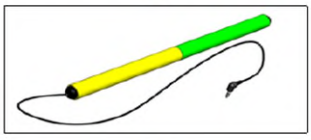
1. SAFIRA consists of 3 separate components. They are the **Sterile Syringe**; the **Driver**; and, the **Foot Pedal** (all 3 are pictured and labelled below).



The Sterile Syringe



Driver



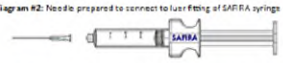
Foot Pedal

2. Attach the Foot Pedal to the Driver. The plug end of the cord goes into the round receptacle opening as shown in **Diagram #1**. Place Foot Pedal on the floor and SAFIRA is ready to receive the Sterile Syringe (see **Diagram #3**)

Diagram #1: Foot Pedal plugged in

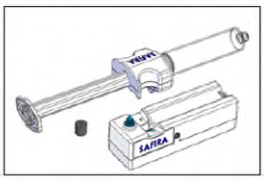
3. Open the sterile package and remove Sterile Syringe. Use normal hospital technique to fill and prepare the syringe.
4. Connect the appropriate needle to the luer fitting of the syringe. Ensure that the needle is connected securely to the syringe. Once secured, prime the needle and tubing set to remove the air.

Diagram #2: Needle prepared to connect to luer fitting of SAFIRA syringe



5. Ready for Sterile Syringe to attach to the Driver; **remove protective foam cap from the Driver gear prior to connecting (see below).** Align Sterile Syringe with Driver as shown in **Diagram #3**. Once aligned, gently press the Sterile Syringe in the Driver. It will be seated correctly when you hear it "click" into place.

Diagram #3: SAFIRA ready for the Sterile Syringe



6. Place the Foot Pedal on the floor below the surgical site in a convenient location for the Anaesthesiologist. See **Diagram #4** for reference.

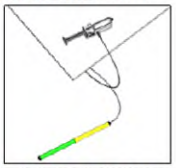


Diagram #4: Foot Pedal placed on floor below surgical site

7. **Removal:** In order to remove the Sterile Syringe from the Driver, simply press the square teal button on the side of the Driver as shown in **Diagram #5**. The Sterile Syringe will immediately release from the Driver.

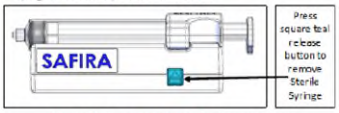


Diagram #5: Press square release button to remove Syringe

7. The Foot Pedal has two colours: **Green** – Infusion; and, **Yellow** – Aspiration as shown in **Diagram #6**.

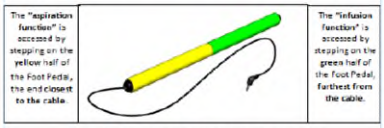


Diagram #6: Foot Pedal showing Infusion and Aspiration functions

8. **Driver Indicator Lights**. On the top edge of the Driver (refer to **Diagram #7**) colour indicator lights are displayed representing various functions in action or functions that require additional action. The indicators are as follows:

LED Colour	State	Meaning	Operator Response
Red	Flashing (Infusion has stopped)	Warning: Immediate response by operator is required	Operator: Infusion has stopped; 1. Verify needle patency and/or reposition needle to allow low pressure infusion 2. Reset SAFIRA (see step 9 #10 and #11 for details)
Red	Steady (Battery is low)	Warning: Immediate response by operator is required.	Operator: Complete the procedure and replace the Driver due to low battery
Green	Steady (Infusion Function Active)	Normal: System operating as designed, indicating infusion activity	Operator: Continue infusion activity until medical result is achieved.
Yellow	Steady (Aspiration Function Active)	Caution: Aspiration occurring – system operating as intended	Operator: Follow Standard Precautions during use of aspiration function
No Active Light	N/A	Normal: System is ready for infusion or aspiration	Operator: N/A

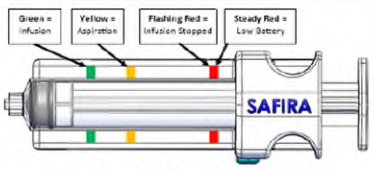


Diagram #7: Top edge of driver, illustrated with all indicators.

9. Begin the procedure following standard hospital guidelines. Throughout the injection SAFIRA is designed to limit the infusion pressure up to a maximum of 20 PSI.

10. Should an infusion stoppage be encountered during the procedure, it may indicate an intraneural injection or a blockage in the fluid path. Verify needle patency and/or reposition needle to allow low pressure infusion and then reset the **Flashing Red Light/Infusion Stopped** on the Driver.

11. To **reset the Flashing Red Light / Infusion Stopped** on the Driver, follow either of the two (2) steps indicated below:

    a. **Aspirate** (Yellow side closest to the cable of the Foot Pedal) until red lights go out: or
    b. **Release Sterile Syringe (see Diagram #5)** and re-click into place

    Now the procedure can be continued.

12. When the procedure is complete, follow standard hospital protocol for the following:

    a. Dispose of the Sterile Syringe using acceptable standard practice for biohazard waste
    b. Driver and Foot Pedal components should be stored according to hospital practice for reuse

13. **Low-Battery Indicator**: Once the Low-Battery indicator on the Driver (steady red lights) comes on, the component should be disposed of in accordance with hospital procedure. Do not start a procedure if the low battery indicator is already on from the beginning. If the Low-Battery indicator lights up during a procedure, there should be enough power remaining to complete the procedure.

Disposal:
For SAFIRA components, follow standard hospital protocol for disposal.

1. **Sterile Syringe:** Use acceptable practice for biohazard waste.
2. **Driver:** Should not be disposed of as unsorted municipal waste. Dispose of unit in line with local guidelines.
3. **Foot Pedal:** Should not be disposed of as unsorted municipal waste. Dispose of unit in line with local guidelines.

Reuse:

The SAFIRA **Sterile Syringe** component **is not reusable** and must be discarded using standard biohazard disposal procedures. The SAFIRA **Driver** component **is reusable** and should be wiped with gauze soaked in at least 70% isopropyl alcohol. The SAFIRA **Foot Pedal** component **is reusable** and should be wiped with gauze soaked in at least 70% isopropyl alcohol.

How Supplied:

The SAFIRA Sterile Syringe component is provided sterile; the contents are sterile unless the package is opened, damaged or the expiry date has been exceeded.

Use Environment:

SAFIRA is designed for use by a physician, in either a hospital or surgical centre environment. The device is not intended to be used outside of stated environments.

Environmental Operating Conditions, Transport and Storage Between Uses:

(Driver and Foot Pedal)

Temperature Range (Product Use): 50F (10C) to 104F (40C)

Temperature Range (Shipping & Handling): 14F (-10C) to 104F (40C)

Humidity Range: 10% to 95%, noncondensing

Atmospheric Pressure: 500 to 1060 Millibars

Device Type:

SAFIRA is a Type BF device.

The SAFIRA components are not conductive and can be immediately released from patient. The needle and tubing (which is not supplied by Medovate) attached to the SAFIRA is the part in physical contact with the patient and can be immediately released from the patient.

Mode of Operation:

Transient.

Power Supply:

Two (2) AAA 1.5V alkaline batteries power the Driver component.

Trouble Shooting:

1. See **Diagram #7** on Page 7 describing actions required should either flashing red light or steady red light appear.
2. ***If unit stops working during the mode of a procedure, simply press the teal button on the side of the Driver component and release the Sterile Syringe. You may complete the procedure using the Sterile Syringe in the traditional manual mode.***
3. Should the Driver component fail to operate either before or during a procedure, please return to Medovate for replacement. ***The device should not be taken apart or repaired by anyone other than authorized Medovate personnel.***
4. Should a serious incident occur during the use of or as a result of the SAFIRA system, please contact Medovate.
5. See Medovate website for details of local Medovate representative.

End of Section

Important Technical Information

Electromagnetic Compatibility (EMC):

This product needs precautions regarding EMC and needs to be installed into service according to the EMC information provided. This unit can be affected by portable and mobile RF communication equipment.

1. Do not use a mobile phone or other devices that emit electromagnetic fields near the unit. They may result in incorrect operation of the unit.
2. **CAUTION:** SAFIRA should not be used adjacent to or stacked with other equipment and that if adjacent or stacked use is necessary, this unit should be observed to verify normal operation in the configuration in which it will be used.

Electro Magnetic Emission:

Guidance and Manufacturer's Declaration: Electromagnetic Emission

SAFIRA is intended for use in the electromagnetic environment specified below. The customer and/or user of SAFIRA should assure that it is used in such an environment.

Emission Test	Compliance	Electromagnetic Environment: Guidance
RF Emissions CISPR 11	**Group 1**	SAFIRA uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.
RF Emissions CISPR 11	**Group A**	SAFIRA is suitable for use in all establishments, other than domestic and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.

Electro Magnetic Immunity:

Guidance and Manufacturer's Declaration: Electromagnetic Immunity

SAFIRA is intended for use in the electromagnetic environment specified below. The customer and/or user of SAFIRA should assure that it is used in such an environment.

Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment: Guidance
Electrostatic Discharge (ESD) IEC 61000-4-2	±8 kV contact ±2, 4, 8, 15 kV air	±8 kV contact ±2, 4, 8, 15 kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.
Power Frequency (50Hz/60Hz) Magnetic Field IEC 61000-4-8	30 A/m	30 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.

Note: U_T is the a.c. mains voltage prior to application of the test level.

Electro Magnetic Immunity: (continued)

Guidance and Manufacture's Declaration: Electromagnetic Immunity

SAFIRA is intended for use in the electromagnetic environment specified below. The customer and/or user of SAFIRA should assure that it is used in such an environment.

Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment: Guidance
Conducted RF IEC 61000-4-6	3V rms (1kHz 80%) 150kHz–80MHz 6V rms ISM and amateur radio bands	3Vrms 6V rms	Portable and mobile RF communication equipment should be no closer to any part of SAFIRA, including cables, than the recommended separation distance of 300mm. Field strength from fixed RF transmitters, as determined by an electromagnetic site survey[a], should be less than the compliance level in each frequency range[b]. Interference may occur in the vicinity of equipment marked with the following symbol:
Radiated RF IEC 61000-4-3	3 V/m (1kHz 80%) 80MHz–2.7GHz	3V/m	

Note 1: The guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

Electro Magnetic Immunity: (continued)

[a] Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which SAFIRA is used exceeds the applicable RF compliance level above, SAFIRA should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orientating or relocating SAFIRA.

[b] Over the frequency range of 150 kHz to 80 MHz, field strengths should be less than 3 V/m.

End of Section

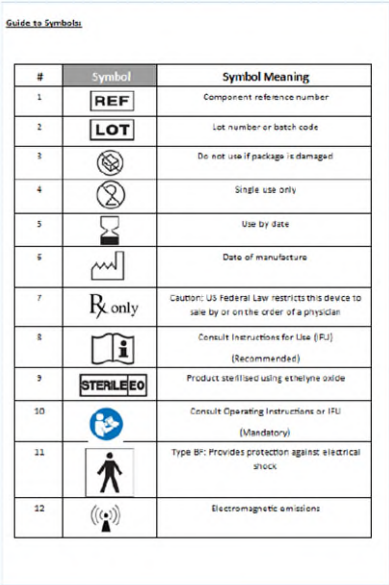
Guide to SAFIRA Reference:

900019 (Component Level—stands for the Sterile Syringe component)

900029 (Component Level—stands for the Driver component)

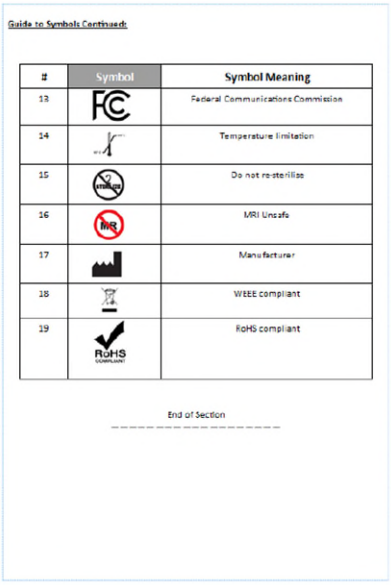
900044 (Component Level—stands for the Foot Pedal Component)

End of Section



Guide to Symbols

#	Symbol	Symbol Meaning
1	REF	Component reference number
2	LOT	Lot number or batch code
3		Do not use if package is damaged
4		Single use only
5		Use by date
6		Date of manufacture
7	Rx only	Caution: US Federal Law restricts this device to sale by or on the order of a physician
8		Consult Instructions for Use (IFU) (Recommended)
9	STERILE EO	Product sterilised using ethelyne oxide
10		Consult Operating Instructions or IFU (Mandatory)
11		Type BF: Provides protection against electrical shock
12		Electromagnetic emissions



Guide to Symbols Continued:

#	Symbol	Symbol Meaning
13	FC	Federal Communications Commission
14		Temperature limitation
15		Do not re-sterilise
16		MRI Unsafe
17		Manufacturer
18		WEEE compliant
19	RoHS	RoHS compliant

End of Section

Warranty Statement:

The product and each component of its system (hereinafter "the product") have been designed, manufactured, tested and packaged with all reasonable care. However, Medovate has no control over the conditions under which the product is used and a disturbance of the intended function of the product may occur for various reasons. In this respect, the warnings in the product publication/instructions for use are expressly to be considered as an integral part of this disclaimer and provide more detailed information. For this reason, Medovate disclaims all warranties, expressed or implied regarding the product, including but not limited to, any warranty of merchantability or fitness for a particular purpose of the product. Product descriptions or user guidelines in publications do not constitute any expressed representation, or any expressed or implied warranty. Medovate is not liable for any direct, incidental or consequential damages or medical expenses caused by any use, defect, failure or malfunction of the product whether the claim is based on contract, warranty, tort or otherwise. This does not apply in the case of intention or in the case of gross negligence of legal representatives or executive staff of Medovate. In commercial transactions relating to merchants, the liability is limited to the compensation of typical damages; compensation for any untypical or incidental damage is excluded. These limitations of liability and warranty are not intended to contravene any mandatory provisions of law applicable in the respective country. If any clause of the disclaimer is considered by a competent court to be invalid or to be in conflict with the applicable law, the remaining part of it shall not be affected and remain in full force and effect. The invalid clause shall be substituted by a valid clause which best reflects Medovates legitimate interest in limiting liability or warranty without infringing any mandatory provisions of applicable law. No person has any authority to bind Medovate to any warranty or liability regarding this product.

SAFIRA...SAfer Injection for Regional Anaesthesia

The SAFIRA is manufactured for:

MEDOVATE
Developing Innovation

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8.2 DD/AE/ADE/SAE/SADE

8.2.1 Device Deficiency (DD)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance including malfunctions, use errors, and inadequate labelling.

8.2.2 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device including events related to the medical device or the comparator and including events related to the procedures involved.

8.2.3 Adverse Device Effect (ADE)

Adverse Event related to the use of a medical device including adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, or operation, or any

malfunction of the medical device and any event resulting from use error or from intentional misuse of the medical device.

8.2.4 Serious Adverse Event (SAE)

Adverse Event that: a) led to death, b) led to a serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolonged hospitalization or, 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NB: Planned hospitalization for a pre-existing condition, or a procedure required as part of standard care, without serious deterioration in health, is not considered a serious adverse event.

8.2.5 Serious Adverse Device Effect (SADE)

Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.