SoBran INC.

# WHITE PAPER:
# POST-APPROVAL MONITORING

## The What, Why and How of Instituting a Professional Post-Approval Monitoring Program

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# INTRODUCTION

Opinions about the effects of the rules, regulations and oversight on today's bioscience laboratories are as wide ranging as there are rats in the *Pied Piper* fairytale. One unifying datum that everyone recognizes is that practical and attentive regulatory compliance not only produces the best animal care, but also reduces further bureaucratic burden and generates more accurate science. The principal result of a professional and rational **Post-Approval Monitoring (PAM)** program helps produce exactly this; a means of understanding what is going on in the program and study, reproducible results, less paperwork and legitimate compliance. Most significantly, this then engenders humanely treated animals and less chance of the authorities visiting your organization. (Figure 1)


Authorities march in on the cruelest kind of animal testing.

Figure 1

In this white paper we suggest that a successfully executed PAM program is one of the best contemporary tools in the bioscientist's toolbox. It is a system that ensures, and verifies; animal care and use (ethics and public relations), institutional compliance (legal), reproducibility (QC), problem solving and improved methodology (better science).

We discuss the what, why and how of PAM, the consequences of non-compliance and the options available to initiate a successful PAM program.

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# WHAT IS PAM?

Post approval monitoring is part of the oversight structure and the responsibility of the IACUC (Institutional Animal Care and Use Committee). By definition therefore, PAM is an accountability process, a potentially very efficient oversight tool for the IACUC ensuring the letter and spirit of the law is being applied and attesting humane animal care.

The standard work of an IACUC is dominated by review and approval of protocols, so instituting a PAM program provides another tool to help with their daily burden without weakening their responsibility or oversight. It actually improves their oversight. It helps make the IACUCs job easier to perform well.

An effective PAM program is designed to produce qualitative and quantitative evidence that everything is working as it should be.

A thoughtful PAM program is not, as many fear, designed to catch people violating rules and the PAM program specialist is not the *protocol police*. An effective PAM program is designed to produce qualitative and quantitative evidence that everything is working as it should be. It also helps uncover problems and enables recommendations of corrective measures. In addition, it generates a semi-formal opportunity for coaching and consultation promoting best practices among the study staff. All in all it is a system that verifies and confirms procedural compliance, uncovers unrecognized non-compliance, and promotes solutions for the betterment of animal welfare and the research. Everyone involved in animal use wants clear evidence and assurance of sufficient oversight and integrity in biomedical research. The PAM program is designed to help provide this assurance.

Viewed negatively, one could describe a PAM program as just another regulatory burden leveled on the scientists and institutes. Undoubtedly it could be a burden, but the small cost a PAM program (or PAM ‘insurance’) requires is well worth the price to reduce the *potential* liability overall.

Most research personnel are strongly committed to animal welfare and would instantly report any negligence. They are aware that healthy animals treated humanely results in far better science. Hence, the majority of non-compliance issues do not originate from nefarious intent; but however well-meaning and attentive a researcher, unfortunate and unintended non-compliance may still cause severe consequences for the animals and

scientist alike. Non-compliance, as we discuss below, is far worse than the 'confirming and learning' engendered by a successful PAM program.

Also, for the naysayers, what must be accepted and understood is that ethically, legally and morally, it is the natural evolution of bioscience research to steadily extend and improve oversight and compliance. Continually increasing our understanding of animal care, increasing public interest, extensive public funding and the litigious nature of current society will regularly drive a change in the requirements for the bioscientist using animals. A well functioning PAM process will offer the IACUC another tool in dealing with future changes to the regulatory burden. Efficient administration of a PAM program is where the benefits of oversight can truly be demonstrated for the animal and researcher alike.

# WHY INSTITUTE PAM?

Aside from the ethical and moral arguments noted previously, there are two main reasons to institute PAM or PAM-like oversight.

The first reason is *'lex terrae'* or in English 'It's the law of the land' (Box 1., NRC 2011). Many laboratories and institutions have had PAM-like programs in place for many years. But as of Jan 1, 2011, in the National Academy of Sciences, '*Guide for the Care and Use of Laboratory Animals*', (The Guide), PAM became the formal standard to abide by for most facilities that use laboratory animals in the USA. As of Jan 1, 2012 continuing IACUC post approval monitoring implementation became required for accreditation and licensing by such agencies as AAALAC and USDA (United States Department of Agriculture); and it is reported that 99 of the top 100 NIH funded institutions are AAALAC accredited. Grant submissions, OLAW assurance documents and PHS policy all require that animal use follow 'The Guide' before using animals in pre-clinical research, drug discovery, or drug development.

***Box 1. Page 33 from The Guide***

***<u>Postapproval Monitoring</u>***

***Continuing IACUC oversight of animal activities is required by federal laws, regulations, and policies. A variety of mechanisms can be used to facilitate ongoing protocol assessment and regulatory compliance.***

The second reason is that a professional PAM program helps individuals and organizations mitigate risk. The risks in question range from small, typically encountered problems requiring corrective action at the IACUC level; to career ending, institutional damaging risk. Real, and in some instances even alleged, non-compliance can threaten research funding, an individual scientist's reputation, and the integrity of a company or institution. For an institution this can affect funding, the ability to attract high caliber scientists or students, and can ripple out *ad infinitum*. Data (all work reviewed and approved by the IACUC must be compliant with the protocol for publication) can be discounted, laboratories damaged and even personal safety threatened by animal rights activists. With the full application of the law of unintended consequences, an accidental non-compliance can not only stop research it can stop a career. For an institute employing researchers with diverse cultural backgrounds; clear, formalized education-based oversight can protect both from inadvertent non-compliance. Further, when large institutes or companies calculate how many individual personnel are carrying out animal research and how many individually approved protocols exist, human error of 1% or less can still generate multiple potential scenarios of non-compliance weekly.

Extrapolating the risks of non-compliance from a single lab can have much broader implications for biomedical research at large. All animal researchers suffer from being tarred with the same brush, "inadequately addressing non-compliance can result in a loss of public trust not only in the institution but also in the research enterprise" (Klein and Bayne, 2007). It is therefore incumbent upon every scientist and research program to have a mechanism by which potential areas of vulnerability or non-compliance can be discovered.

## What is Required for PAM?

Currently there are no standard requirements for what makes up a PAM program although many articles exist discussing the topic (e.g. Banks & Norton 2008, Plante & James 2008, Collins 2008). The Guide is very clear in its "must do's" but suitably vague in its "should do's", and lists ideas in the broadest sense that consist of all types of protocol monitoring after initial IACUC protocol approval. Guidance can often be understood as *de facto* in research, and industry standards for PAM appear to be evolving based directly upon 'The Guide's' recommendations.

Recommendations include, but are not limited to:

1. Help ensure animal well being
2. Improve and/or refine research procedures
3. Ensure compliance with regulatory agencies
4. Visit and inspect laboratories
5. Review protocols annually
6. Observation of selected procedures and comparison with approved protocols
7. Observation of animals
8. Assess animal and veterinary care
9. Examination of surgical areas
10. Review handling of controlled substances and regulatory compliance per the DEA
11. Review health and safety issues that are protocol related
12. Review records, including, but not limited to, anesthetic, surgical, and training records
13. Review of adverse or unexpected experimental outcomes affecting the animals

The wide ranging responsibility of compliance coupled with *some* grey areas makes this list appear onerous. It may even leave devoted, logic-driven scientists to feel as if they are up the water maze without a paddle. Confounding this are the numerous reports detailing increased regulatory burden (pre-clinical and clinical) as one of the fastest rising costs in universities and drug development today (Glickman *et al* 2009,Goldman *et al* 2008). But here is where prudence and logic can be applied by an experienced PAM specialist and a thorough PAM program. Balancing risk and burden requires experience and clear communication with all stakeholders. Perceived, or real, oversight regardless of cost or outcome may divert money away from research to bureaucracy and alienate researchers; something many IACUC members may have personal experience dealing with already.

With the legal necessity for ongoing oversight, potential consequences, and extensive requirements of animal use in research, how can an effective, professional PAM program be introduced?

# How Can a PAM Program Be Introduced?

There are two practical options to institute a professional PAM program. The first is to directly hire the respective personnel who define and develop the program, and carry out its implementation. The second, and arguably most efficient and cost effective way, is to outsource the function to a professional PAM service company.

A full time employee overseeing PAM is a large financial burden on research grants or company funds. In addition, hidden fees, paper work and time associated with finding, employing and managing new personnel costs money; not just immediately but continually and for the length of the position. As the function of an oversight program is required legally, this may be a very long time. Problems associated with a poorly performing employee can further generate time consuming and lasting issues of *HRstorical proportions.

The PAM program will be drafted by a recognized expert instituting a standardized and transparent system that is adaptable to the needs of the institute and laboratory in question.

A better alternative may be an external PAM specialist, acting just like a regular auditor under the supervision of the IACUC and tasked with representing them. The PAM program will be drafted by a recognized expert instituting a standardized and transparent system that is adaptable to the needs of the institute and laboratory in question. Audits can be implemented when required, as quickly as required, with no need for institutional human resource management and adjusting to a laboratories schedule. The external PAM specialist is responsible for coordinating visits, generating clear and thorough reports in a timely fashion, most correspondence, maintaining records, and providing training and support as required assuring compliance. They can be involved in policy and procedure meetings as well as sitting on the IACUC as a voting or *ex-officio* member. The PAM specialist will act as a liaison between the IACUC and the study staff. Most of all they can serve as an institutional and informational resource too. A service company's commitment to customer service also needs to be acknowledged as a real plus when considering the requirements of a PAM program.

External monitoring from a third party also decreases the likelihood of conflicts of interest and enhances the public perception. Unfortunately, there is a never ending stream of news articles pointing out these conflicts, detailing animal abuse and casting a poor light on the industry (AWI Q, 2013). An external partner lends another level of credibility that self-regulation does not. Unfair though that contention may be, the terminology of big-bank self-regulation, wall-street self-oversight and government self-investigation all summon a sentiment of mistrust. Likewise, animal welfare self-oversight does not provoke the level of comfort in the public we in the industry know it implies.

## What is Required of a PAM Specialist?

The PAM specialist administering the PAM program, by definition of the function, requires a certain education, skill set, level of experience and a specific personality with the understanding of the unique requirements and central position of the role (Figure 2). They may be veterinarians, credentialed veterinary technicians (RVT, CVT, LVT,) certified AALAS technicians (ALAT, LAT, LATG) or CPIA (certified professional IACUC administrator). When assessing viable candidates either as a potential employee or from an expert service provider ensure the following characteristics are satisfied:

- Knowledgeable and experienced in the subject matter. Qualifications should minimally include a diploma or B.S. degree in the life sciences, at least 10 years' experience in the lab animal science field, previous experience sitting on or running an IACUC, experience in training, writing protocols or SOPs and a complete knowledge of all current regulatory policies and rules.
- An excellent communicator and possessing a friendly, professional outlook and demeanor in potentially challenging circumstances
- An ability to be diplomatic yet firm when delivering news of corrective actions
- An ability to give recommendations of improvements without being overly authoritative
- Someone who not only understands the requirements but also knows how to meet both the letter and the spirit of the regulations
- Someone who understands how to align federal and institutional regulations to the pursuit and support of scientific research


Figure 2 The central role of the PAM Specialist and PAM Program

# THE PAM AUDIT DEFINED

Whether an external expert is chosen or an internal employee is tasked with the challenge of implementing a well thought out PAM program, the oversight breaks down into its simplest functional unit of a PAM visit or audit. The audit can be requested at any time, performed on any randomly selected active protocol, any protocol at the discretion of the IACUC staff/attending veterinarian, or any protocol complimentary to IACUC semi-annual inspections. Of course an audit may also be requested resulting from a report of a serious non-compliance issue. Although contrary to public perception, compared to the amount of research carried out, this is relatively rare. Prior to the visit a letter of intent is sent to the PI whose work is being audited.

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**An example Pre-PAM visit letter is shown below.**

*Dear Dr._____*

*In accordance with your Institutional Animal Care & Use Committee (IACUC) I have been employed to perform post-approval monitoring (PAM) at the approved animal care and use facility where you currently perform research. The goal of this appointment is to solely gather evidence of good performance and conclude with an approval for your laboratory for adherence to the approved animal use protocol/s.*

*This process is designed and anticipated to be collegial and supportive of your animal based research at your designated facility. The goal of the PAM program is to serve as the 'eyes and ears' of the IACUC.*

*I will work diligently to facilitate your research and help your laboratory understand and stay fully compliant with the expectations of the animal care and use program at _____.*

*This appointment is regarding your protocol/s titled _____ protocol#_____*

*Whilst I may provide your laboratory expert counsel and/or advice and may encourage your laboratory to consider specific corrective actions, the Principal Investigator for the protocols identified above remains obligated to submit any required amendments, reports, or explanations of on-going activities.*

*After completing the protocol audit, I will provide a 'Conclusion Briefing' to an assigned member of your laboratory or yourself. The function of this 'Conclusion Briefing' is to confirm the accuracy of the observations. Protocol deviations or problem conditions will be shared with the laboratory staff member(s) present during the 'Conclusion Briefing'.*

*Within 24 hours of this appointment, an email will be sent to you, the Principal Investigator and IACUC describing the outcome of this visit, identifying any items that may require corrective attention. You should initiate corrective actions, if any, in response to this email.*

*Attached is the PAM worksheet so you can review the items I will be focusing on.*

*The IACUC and your fellow scientists appreciate your support to assure the integrity of the animal research enterprises of the institution.*

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Once the pre-scheduled PAM Specialist arrives and formalities are completed, a number of observations are made and documented before, during and after the execution of the defined protocol. Appendix 1 is an example of a typical form. A short web search will yield multiple further examples.

Following the visit, a discussion of the results and conclusions are shared with the PI for cross reference, further information and feedback. Typically within 24-48 hours a communication (most likely email) will be sent to the PI and IACUC officially relaying a detailed summary of the findings.

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**Below is a typical example of the communication for a successful visit without any non-compliance issues.**

*Dear Dr._____*

*On the, DATE, a routine animal program review of the activities approved under the protocol identified above was conducted by _____, on behalf of the _____ Institutional Animal Care and Use Committee (IACUC).*

*With respect to the procedures covered under this protocol, all procedures observed were performed as approved in the protocol. Please commend your staff for the attention to detail, the professional manner*

*in which the animal activities were conducted, and the humane manner in which the animals were handled.*

*Successful reviews such as this provide clear evidence of institutional regulatory compliance, as dictated by the Animal Welfare Act and the Public Health Service Policy. Thank you and your staff for your cordial hospitality and the support of your institution's commitment to quality care and progressive research. Congratulations on a job well done!*

*A copy of this memo note will be maintained in the IACUC office.*

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**Below is a further example of a letter to a laboratory where some non-compliance issues were acknowledged.**

*Dear Dr. _____,*

*On the, DATE, a routine animal program review of the activities approved under the protocol identified above was conducted by _____, on behalf of the _____ Institutional Animal Care and Use Committee (IACUC).*

*Thank you for your collegial manner in assisting with this program audit.*

*Monitoring experimental animal procedures post-approval is one method the Institutional Animal Care and Use Committee (IACUC) uses to assure many regulatory agencies that animal studies are conducted in accordance with approved _____IACUC protocols, as dictated by the federal Animal Welfare Act, Public Health Service Policy, and the NRC's Guide for the Care and Use of Laboratory Animals.*

*With respect to the procedures observed under this project, the following issues require attention:*

*OBSERVATION: Isoflurane Vaporizer – The Isoflurane machine was last calibrated 01/01/10.*

*SUGGESTION: Anesthetic machines should be calibrated annually. Please have this machine calibrated as soon as possible. This was mentioned to _____, assigned to be present during the audit.*

*OBSERVATION: Isoflurane Levels – Isoflurane was used at a level of 5% for induction of anesthesia, and then reduced to 2% for maintenance during the procedure.*

*SUGGESTION: The approved IACUC protocol states that Isoflurane will be used at 1-2% concentration during each surgery. It is recognised that this level would not be sufficient for effective induction of anesthesia. However, because the protocol was not followed specifically this is an issue of non-*

*compliance with the protocol. As a result, please submit a letter detailing this issue to the IACUC along with an amendment to the IACUC protocol detailing the Induction and Maintenance level of Isoflurane used throughout each procedure.*

*OBSERVATION: Use of Vetbond in lieu of surgical sutures or staples.*

*SUGGESTION: The approved IACUC protocol states that surgical sutures or staples will be used to close the incision made for mini pump implantation. This was mentioned to _____, assigned to be present during the audit. She stated that the decision was made to switch to Vetbond Tissue Adhesive because the animals were pulling out the sutures before they could be removed. This decision is noted as being made in the best interest of the animals; however, it remains an area of non-compliance compared to statements in the IACUC protocol. Please note that the IACUC must be notified prior to any changes to a protocol. Please submit an amendment to the IACUC detailing the change from surgical sutures to Vetbond adhesive.*

*We realize that certain observations may not be entirely accurate, and we encourage responses which can clarify information obtained during the PAM audit. For the observations that are accurate, please provide a response within 48 hours and include a plan of correction.*

*We also realize that on occasion, research may drift from the original proposal - indeed the very nature of research requires original and creative thought and may become unintentionally non-concordant with the original approval. When non-compliant activities are identified, the research laboratory must either return to the original approved protocol or suspend the change and submit an amendment request to the IACUC for their consideration and approval.*

*Thank you for your consideration, clarification, and response of these items. Our audit is not intended to be negative, but rather a collegial review of approved activities, and an opportunity for education*

*and information sharing of the research process and expectations for research at _____. The IACUC appreciates your adherence to the procedures in the approved protocol until any proposed amendments are reviewed and approved.*

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Based on the facility requirements, follow-up reports, letters and additional comments may be necessary. The IACUC would be made aware of all findings as would the PI. Deficiencies are given a deadline (issued by the IACUC) for correction. The common problem areas most often observed are: exceeding the approved animal numbers, unapproved euthanasia method, improper or no PPE, protocol drift, failure to add new personnel, failure to monitor animals post-procedure and a failure to maintain adequate breeding records.

As with any regulatory-based type of inspection there are also a variety of consequences. Depending on whether findings are minor or major and would be "reportable" (i.e. required to notify the USDA or OLAW), the stronger consequences could include, but are not limited to:

1. Removing personnel from the protocol until further training
2. Putting the protocol on hold until deficiencies are fixed
3. Revoking the protocol
4. Revoking the PI's access to the vivarium
5. No further animals can be ordered or supplied
6. Removal of the PI from the project permanently
7. Loss of DEA license
8. USDA fines
9. Loss of OLAW assurance
10. Loss of grant money or ability to apply for future grants

Even with the severity of the potential consequences listed above, PAM specialist visits are customarily informal and friendly and provide an opportunity for the PI to request any help they may need.

# CONCLUSION

For the bioscientist using animals in research, instituting a program of professional continued oversight is not only required by law, it is also the best insurance to provide optimal animal care and mitigate risk in a highly regulated arena subject to human error.

PAM should be viewed as an outstanding tool employed to help animal and researcher alike perform the best science and in the most humane manner. A professional PAM program is a friend to all. There is a financial and time cost associated with a PAM program but this is much less expensive than a serious non-compliance issue that brings any of the regulatory agencies to your doorstep.

Further, logical efficiencies are continually being suggested (Shalit, 2013). PAM also provides better Quality Control; documenting regularly occurring mistakes and providing for feedback on the success and failures of policies and procedures. Accountable regulatory compliance also engenders public trust.

As indicated earlier, the PAM specialist is neither the research police nor a replacement for the IACUC. The personnel involved should have years of research and regulatory experience and have an understanding of what is required to perform and promote research within the boundaries of local and federal requirements.

Whether you take the time and responsibility to employ and define your own personnel and PAM program or engage one of the efficient and professional service providers to determine and administer the program, a focus on regulatory compliance, scientific integrity and transparent documentation will ensure the system performs as well as it was intended. PAM should be embraced as a great tool to help every entity involved in animal research.

# APPENDIX

| General Compliance | |
|---|---|
| **The Protocol and Personnel** | |
| Does the PI have the most recent version of the complete protocol, including amendments? | |
| Do the laboratory personnel have easy access to the most recent version of the complete protocol, including amendments? | |
| Have the investigators read the protocol? | |
| Are the people performing the study listed on the protocol? | |
| **Study Procedures** | |
| Does the protocol number on the animal's cage card match the protocol number? | |
| Are the procedures performed consistent with those in the approved protocol? | |
| Are lab personnel appropriately trained to perform these procedures? | |
| Are investigators wearing PPE and/or other attire (e.g. masks & gloves) appropriate for the species and procedures performed? | |
| **Anesthesia** | |
| Are the methods of anesthesia in compliance with the protocol? | |
| Are anesthetized animals monitored according to the approved method in protocol? | |
| Are the animals maintained at an appropriate depth of anesthesia for the procedure performed? | |

| | |
|---|---|
| If inhalant anesthetics are used, are they scavenged properly? | |
| Are anesthetic machines serviced and calibrated? | |
| **Surgery** | |
| Is surgery performed in a location that has been approved by the IACUC? | |
| Is the location and method of animal prep appropriate and in accordance with the approved protocol? | |
| Is survival surgery performed using sterile instruments, sterile gloves, a surgery mask, and aseptic technique? | |
| Are intraoperative monitoring sheets being used appropriately? | |
| Is an appropriate heat source used to keep the animal warm throughout the procedure? | |
| Are incisions closed appropriately and in accordance with the approved protocol? | |
| Is there an appropriate recovery area for the animals? | |
| **Post-Surgical Care** | |
| Is post-surgical care in compliance with the protocol? | |
| Are the methods of analgesia (dose, frequency, duration) consistent with the approved protocol? | |
| Is post surgical (post procedural) care adequately documented? | |
| **Euthanasia** | |
| Does the method of euthanasia correspond with what is written in the protocol? | |
| Is death assured by performing an appropriate physical method of euthanasia when required? | |

| **General Record Keeping** | |
|---|---|
| Is there an up to date and complete surgical log? | |
| Are animals identified by protocol number and individual numbers or cage cards? | |
| Are medical and post-procedural care progress notes complete and accurate? | |
| Is medication administration accurately documented? | |
| Are injections, blood collection, and fluid collection amounts dated and documented? | |
| **Laboratory** | |
| If animals are housed in the lab for greater than 12 hours, has the lab been approved by the IACUC? | |
| Are drugs, suture materials and other items within the noted package expiration dates? | |
| Are controlled substances stored appropriately? | |
| Are there any safety issues or other concerns that pose a threat to human or animal safety and welfare? | |

| Protocol Specific Compliance | | |
|---|---|---|
| | **Approved Protocol** | **Observation** |
| **Personnel on Protocols** | | |
| **PPE Worn** | Lab Coat or gown<br>Shoe Covers<br>Surgical masks<br>Gloves<br>Blue plastic gown<br>Face shield or goggles | Lab Coat or gown<br>Shoe Covers<br>Surgical masks<br>Gloves<br>Blue plastic gown<br>Face shield or goggles |
| **Blood Sampling** | Technique: | Technique: |
| | Sample site: | Sample site: |
| | Volume per sample | Volume per sample |
| | Frequency & duration of sampling: | Frequency & duration of sampling: |
| **Urine/feces sampling** | Method: | Method: |
| | Frequency & duration of sampling: | Frequency & duration of sampling: |
| **Collection of tissues** | Tissues collected: | Tissues collected: |
| | When collected (before or after euthanasia): | When collected (before or after euthanasia): |
| | Disposition of collected tissues: | Disposition of collected tissues: |

| | | |
|---|---|---|
| **Indwelling catheters or implants** | Site: | Site: |
| | Type & Size: | Type & Size: |
| | Maintenance: | Maintenance: |
| | Duration: | Duration: |
| **Tumors, transplanted or induced** | Site: | Site: |
| | Type & Size: | Type & Size: |
| | Maintenance: | Maintenance: |
| | Duration: | Duration: |

| Anesthesia and Analgesia | | | | |
|---|---|---|---|---|
| | Dose (mg/kg) | Route | Frequency | |
| **Sedatives/Tranquilizers** | | | | |
| | | | | |
| | | | | |
| **Anesthetics - General** | | | | |
| | | | | |
| | | | | |
| **Anesthetics - Local** | | | | |
| | | | | |
| **Analgesics** | | | **Frequency** | **Length of Administration** |
| | | | | |
| | | | | |
| **Antibiotics** | | | | |
| | | | | |
| | | | | |
| **Miscellaneous** | | | | |
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Figure 1. Kindly reproduced with the permission of comedian and syndicated cartoonist Jason Love at jasonlove.com

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*HRstorical is not currently listed in any English dictionary of note but since writing this paper the portmanteau has had universal acceptance in its application.