Clinica Chimica Acta xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Harmonization of critical result management in laboratory medicine

C.A. Campbell [a], A.R. Horvath [a,b,c,*]

[a] SEALS Department of Clinical Chemistry, Prince of Wales Hospital, Sydney, NSW 2031, Australia
[b] Screening and Test Evaluation Program, School of Public Health, University of Sydney, Sydney, NSW 2031, Australia
[c] School of Medical Sciences, University of New South Wales, Sydney, NSW 2031, Australia

ARTICLE INFO

Article history:
Received 2 September 2013
Received in revised form 6 November 2013
Accepted 7 November 2013
Available online xxxx

Keywords:
Alert result
Critical result
Laboratory medicine
Patient safety

ABSTRACT

Unsafe medical care is a major source of disabling injuries and death throughout the world. The failure to notify, follow up, and action critical results, which signify life threatening situations, is of particular concern and may cause avoidable morbidity and mortality. International accreditation standards require pathology laboratories to have a system for the timely and reliable communication of critical results to clinical personnel responsible for patient care. In response, various practices and a number of different terminologies have been described in the literature. Increased attention to patient safety standards and multinational surveys, however, highlighted shortcomings and inefficiencies in existing communication systems. These failures and variations in practice call for clear guidance and harmonization of approaches in order to improve communications and to provide safer patient care. The objectives of this review are to create a harmonized terminology and to learn from international practices by systematically reviewing the best available evidence on existing approaches. Based on literature review findings we highlight key areas where harmonization is necessary and feasible and offer a conceptual framework and methods for designing better and more evidence-based systems for the timely notification of laboratory results that represent potential patient safety hazards.

1. Introduction

Medical tests should only be requested if the results of the tests will be used to influence subsequent management decisions of the patient. As trivial as it may sound, laboratory professionals all over the world know too well that many of the test results that are released to clinicians in vast numbers with rapid turn-around times are not followed up in a timely manner and may have no beneficial impact on patient management. This is of particular concern when critical results are involved, as they signify situations which may be life threatening or lead to irreversible damage or harm to the patient and which therefore require immediate or timely medical intervention. Unsafe medical care is a major source of disabling injuries and death throughout the world. In 2008 a report, published by the World Health Organization World Alliance for Patient Safety, identified poor test follow-up as one of 23 topics that have a substantial impact on the safety of medical care [1]. The rate of test follow-up was found to be suboptimal across the globe, with communication of test results between the laboratory and physicians being one area that needs improving. A systematic literature review of evidence between 1990 and 2010 revealed a lack of test follow-up for up to 60% of hospital inpatients, and up to 75% for patients treated in the emergency department [2]. Critical test results were identified as one area where problems were particularly evident. In the United States the National Quality Forum's list of serious reportable events in 2011 included two new laboratory-related errors leading to serious injury or death of patients. One of these reportable errors was due to the failure to follow-up or communicate laboratory, pathology or radiology results [3]. In 2010, the Clinical Excellence Commission Patient Safety Team analyzed data collected from the New South Wales Incident Information Management System to review and identify how access and follow-up of diagnostic test results affected patient outcomes [4]. Findings of the review indicated that failure in processes associated with obtaining and using diagnostic test results has the potential to seriously compromise patient safety. Issues identified included timeframes for test reporting being poorly defined and unrelated to clinical urgency; pending results that are potentially critical never being reviewed by the treating team; no consistent mechanisms exist for clinicians to identify critical results which have not been reviewed; and considerable variability in the process for communicating unexpected or significantly abnormal results.

Automation and information technology revolutionized the delivery of laboratory services and we have almost limitless opportunities to communicate test results on various devices faster and closer to the clinician and patient than ever before. Paradoxically, the vast amount and rapid flow of data contribute to information overload and communication breakdowns and, as a consequence, to increasing medical error

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine; ISO, International Organization for Standardization; USA or US, United States of America; UK, United Kingdom; WHO, World Health Organization.

* Corresponding author at: SEALS North, Department of Clinical Chemistry, Level 4, Campus Centre, Prince of Wales Hospital, Barker Street, Randwick, Sydney, NSW 2031, Australia. Tel.: +61 2 9382 9078, +61 404 027 843 (mobile); fax: +61 2 9382 9099.
E-mail address: rita.horvath@sesiahs.health.nsw.gov.au (A.R. Horvath).

0009-8981/$ – see front matter.
http://dx.doi.org/10.1016/j.cca.2013.11.004

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004

rates. Therefore laboratories have even greater responsibility of controlling post-analytical and post–post-analytical processes and offering solutions that help to reduce medical error rates and improve the effectiveness and timeliness of medical decisions [5].

It was over 40 years ago that Dr George D. Lundberg reported the implementation of the first formal critical result communication system in Pathology at the Los Angeles County USC Medical Center. Lundberg coined the term 'critical result' as a laboratory test result representing a pathophysiologic state so abnormal that it is life-threatening if action is not taken quickly and for which an effective action is possible [6]. A short list of critical limits (i.e., upper and/or lower thresholds for a test outside of which a result would be critical) was compiled, and once a critical result was recognized by a laboratory technologist, it became the responsibility of the laboratory to urgently and personally communicate it to the physician responsible for the patient. Although not initially published in a peer-reviewed journal, the critical result system gained rapid acceptance [7]. It was widely implemented in a very short time and soon became a laboratory accreditation requirement [8–11]. Lundberg claims that the rapid success of his critical result system was largely due to the initial critical list only containing limits that were clearly life threatening [7]. Subsequently, Lundberg proposed that laboratories should also have a system for communicating important (according to his terminology "vital") but less urgently reportable results [12].

Since Lundberg's pioneering work and in response to accreditation requirements, many laboratories have implemented critical result communication systems. Various practices and a number of different terminologies have been described in the literature, while increased attention to patient safety standards highlighted shortcomings and inefficiencies in existing communication systems. These failures and variations in practice triggered a number of national organizations to investigate their current practices and, based on findings, formulate recommendations for a more harmonized and systematic approach for notifying clinicians about abnormal test results that need urgent or timely medical attention. These published multinational surveys and recommendations provide the backbone of this review. We will discuss in more detail below what can be learnt from the synthesis of the evidence and how that information can support global harmonization initiatives in this area.

The objectives of this review are to 1/create a harmonized terminology; and 2/reflect on the current status of international practices. Based on findings of the review of the literature we 3/highlight key areas where harmonization is necessary and feasible; and 4/offer a conceptual framework and methods for designing better and more evidence-based systems for the timely notification of laboratory results that represent potential patient safety hazards.

2. Need for harmonized terms and definitions

Singh and Vij have made eight very useful practical recommendations for policies and practices of communicating abnormal test results [13]. Their first recommendation emphasizes the importance of clear definitions in order to provide credibility to the policy and to ensure a common understanding across a broad range of users. For clarity and harmonization of terminology we present currently used and published definitions together with their most common alternative synonyms and our proposed terms (Table 1).

Current patient safety goals require timely communication and follow-up of abnormal diagnostic test results to avoid medical errors, adverse events, and liability claims [13]. There is significant confusion in this area of what type of laboratory tests and results should be communicated to clinicians and how one should define the various categories of abnormal test results that need urgent or timely clinical notification. Due to differing clinical significance and priority, similarly to a number of authors [12,13], we highlight the importance of clearly differentiating life-threatening *critical results* from non-life threatening *significantly abnormal results*. *Critical results* may signify a pathophysiologic state that is potentially life threatening or that could result in significant patient morbidity or irreversible harm or mortality and therefore requires urgent medical attention and action [6,10,13–16]. *Significantly abnormal results* are not life threatening but they require medical attention and follow up action within a medically justified timescale, and for which timing is not as crucial as for critical results (Table 1) [12,13]. We suggest that no terms that refer to 'values' (i.e. critical, panic, crisis, alarm value) are used as not all laboratory results that need notification have quantitative values (e.g. microbiological cultures or semiquantitative tests are reported as positive or negative). We also propose that terms such as 'panic' or 'crisis' or 'alarm' are avoided because they suggest that no systems are in place for managing such results in a professional manner.

A simple umbrella term for these various categories of notification priorities would be helpful but no terms in the literature seem to be appropriate so far. The various meanings of the term 'alert' may probably be more suitable as this term describes in the broadest sense the actual problem and the typical actions that follow. In addition, this word can be used as a noun, adjective and verb and provides flexibility in describing subsequent definitions discussed below. According to various dictionaries the noun 'alert' refers to i) a signal that warns of danger; ii) a condition or period of heightened watchfulness or preparation for action. As an adjective it means i) vigilantly attentive, watchful; ii) mentally responsive and perceptive; iii) quick (http://www.thefreedictionary.com/alert); iv) watchful and prompt to meet danger or emergency; or v) quick to perceive and act (http://www.merriam-webster.com/dictionary/alert). As a verb it means to alarm, forewarn, inform, notify, signal, or warn someone (http://dictionary.reverso.net/english-synonyms/alert). We propose using the umbrella term of *alert results* and in this review we will also refer to this term when we discuss policies and practices related to both critical and significantly abnormal laboratory results. We propose retaining the well-embedded terms of 'critical results' and 'significantly abnormal results', when reference is specifically made to such scenarios and practices.

Critical test refers to a test that requires rapid communication of the result to guide further management decisions of medical urgency irrespective whether it is normal, significantly abnormal or critical [13] — e.g. troponin results in all requests from the emergency department, paracetamol results in suspected overdose cases, hematology and coagulation results in suspected disseminated intravascular coagulation, xanthochromia results in suspected subarachnoid hemorrhage, methotrexate results to guide the optimal timing of leucovorin rescue, or tests in cerebrospinal fluid when meningitis is investigated.

Kost and Hale define *critical limits* as the lower and upper boundary values of diagnostic test results that represent life-threatening and also actionable knowledge for clinical therapeutic decisions [17–19]. This term has many synonyms, such as critical value limit, alarm or alert limit, critical or alert interval or range, critical decision limit or threshold, etc. (Table 1). Some authors propose the term, 'action limits' [16], but we (would prefer to) believe that all laboratory results requested, irrespective of their degree of abnormality, will lead to some form of medical decisions or actions, even if the decision or action is only watchful waiting or monitoring. In our view none of these alternative terms encapsulate the current requirements of achieving better patient safety goals by notifying not just life-threatening (i.e. critical) but also medically important, non-life-threatening (i.e. significantly abnormal) results. Another shortcoming of the current definitions is that they refer to single critical limits and do not include rapid changes in test results which could also be critical or significantly abnormal requiring timely medical intervention. Therefore we propose broadening this term to *alert thresholds* which define the upper and/or lower thresholds of a test result or the magnitude of change in a test result within a critical or clinically significant time scale beyond which the finding is considered to be a medical priority warranting urgent or timely action. We prefer using the word threshold rather than limit as, according to the

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004

Table 1
Key definitions.

Commonly used term	Alternative terms	Published term/definition	Source	Proposed term/definition
Critical result	– Critical value – Panic value – Crisis value – Critical alarm – Alarm value	A *critical* (*or panic*) *laboratory value* is a laboratory test result that represents a pathophysiologic state at such variance with normal as to be life-threatening if an action is not taken quickly and for which an effective action is possible.	[6]	*Critical result*: A test result which may signify a pathophysiological state that is potentially life threatening or that could result in significant patient morbidity or irreversible harm or mortality and therefore requires urgent medical attention and action.
		Critical result: Any result or finding that may be considered life threatening or that could result in severe morbidity and require urgent or emergent clinical attention	[13]	
		A *critical test result* is defined as those values or interpretations that, if left untreated, could be life threatening or place the patient at serious risk.	[14]	
		Critical test results: any values/interpretations for which delays in reporting can result in serious adverse outcomes for patients.	[15]	
		Alert or critical values are those results that may require rapid clinical attention to avert significant patient morbidity or mortality.	[10]	
		Markedly abnormal laboratory test result: a result that may signify a pathophysiological state that may be life-threatening or of immediate clinical significance and that requires urgent action.	[16]	
Significantly abnormal result	– Vital result – Life-altering result – Alert value – Markedly abnormal result of medical significance	A *vital value* is a laboratory result just as important as a critical value, but one for which timing is not as crucial.	[12]	*Significantly abnormal result*: A test result that is not life threatening but that requires a timely medical attention and follow-up action within a medically justified timescale.
		Significantly abnormal result: No-emergen , non-life-threatening results that need attention and follow-up action as soon as possible, but for which timing is not as crucial as critical results.	[13]	
Critical test		*Critical test*: Tests that require rapid communication of results, whether normal, abnormal, or critical	[13]	*Critical test*: A test that requires rapid communication of the result irrespective whether it is normal, significantly abnormal or critical.
Critical limit	– Critical value limit – Alarm limit – Alert limit – Action limit – Critical or alert interval or range – Critical decision limit or threshold	*Critical limits* define the lower and upper boundary values of diagnostic test results that represent life-threatening and also actionable knowledge for clinical therapeutic decisions.	[17]	*Alert thresholds*: The upper and/or lower threshold of a test result or the magnitude of change in a test result within a critical or clinically significant time scale beyond which the finding is considered to be a medical priority warranting urgent or timely action.
		Critical limits reflect medical thresholds for emergency patient evaluation and optimization decision points for critical care	[17]	
		Critical or alert limits are the values of laboratory measurements that are regarded as requiring urgent clinical attention and should be communicated to a clinician urgently.	[19]	
Critical list				*Alert list*: A list of laboratory tests, including critical tests and non-critical tests with alert thresholds for critical and/or significantly abnormal results that reflect an agreed policy between laboratory and clinical staff for rapid communication within a pre-specified time frame and according to a procedure.

Table 2
National surveys on critical result management practices.

Procedures	National surveys							
	US 2002 [22] (n = 623)	US 2008 [23] (n = 121)	US 2008 [24] (n = 731)	Italy 2010 [25] (n = 90)	Spain 2010 [26] (n = 157)	Thailand 2010 [27] (n = 242)	Australia 2012 [28] (n = 58)	China 2013 [29] (n = 599)
Source of critical thresholds								
Literature				57%	48%		59%	
Consultation with clinicians	73%			21%	10%		41%	13%
When notification is not required?								
Result similar to previous	12%	36%					80%	<30%
Identification of critical results								
Retest sample to confirm result		All results — 56% Some results — 31%				Private — 100% Govt — 100%		>85%
Mode of notification								
Telephone	99%			89%	91%	Private — 89% Govt — 94%	Inpatients — 96% Outpatients — 92%	95%
Fax	30%			9%	17%	Private — 4% Govt — 1%	Inpatients — 40%[a] Outpatients — 60%[a]	0%
Computer				18%	6%	Private — 30% Govt — 20%	EMR[b] alert — 4%	
Who should deliver critical results?								
Laboratory technician	Inpatients — 91% Outpatients — 77%	99%	91%	11%	Scientist or pathologist — 87%		~ who performed test — 67%	>90%
Section head	Inpatients — 3% Outpatients — 4%						67%	
Laboratory manager/director			8%	69%				
Doctor on call/duty				14%			29%	
Call center		10%	18%	0%			2%	
Who should receive critical results?								
Requesting physician or physician caring for patient	Inpatients — 9% Outpatients — 17%	93%	75%	Inpatients — 37% Outpatients — 80%	87%		96%	95%
Physician on call	Inpatients — 4% Outpatients — 7%			Inpatients — 18%				
Nurse	Inpatients — 56% Outpatients — 35%	91%	62%	Inpatients — 29%	3%		75%c	0%
Timeliness of reporting								
Delivery within set time limits		61%[c]			38%		54%	
Acknowledgement of receipt of result								
Read back of result			91%	62%		Private — 81% Govt — 72%	46%	
Recording result notification								
Requirement to record result notification		99%		58%		Private — 65% Govt — 74%		

n: number of laboratories participating in the survey
[a] Mode of transmission — by fax or email
[b] EMR — electronic medical record system
[c] Timeframe approved by clinicians within last 12 months

Oxford Dictionary, threshold refers to the "magnitude or intensity that must be exceeded for a certain reaction, phenomenon, result or condition to be manifested" (http://oxforddictionaries.com/definition/english/threshold). This generic definition encapsulates the impact on test results and the consequences in patient's condition once a threshold is exceeded. In the same dictionary, *threshold level* is defined as "the level at which one starts to feel or react to something". Again, we find that this definition covers both how the patient may be affected and how the laboratory personnel and clinician should react when alert threshold levels of certain laboratory tests are reached or passed. Different alert thresholds applicable to critical and significantly abnormal results and for different clinical scenarios and settings, as well as allocating different priorities and timescales to their communication will be discussed in later chapters.

In the same vein, we propose the use of the broader term of alert list to replace the term of *critical list*. In the context of laboratory medicine, *alert list* refers to a list of laboratory tests, including critical and non-critical tests with alert thresholds for critical and/or significantly abnormal results that reflect an agreed policy between laboratory and clinical staff for rapid communication within a pre-specified time frame and according to a procedure.

3. Need for harmonized policies and procedures

As mentioned earlier, international accreditation and patient safety standards require pathology laboratories to have a system for the timely and reliable communication of alert results to clinical personnel responsible for patient care [8–11]. Such systems should address the following issues:

- who should define alert lists;
- what should be defined in alert lists;
- how alert results are verified;
- what is the timeframe of communication;
- what communication channels are used for delivering alert results;
- who should deliver and receive the results;
- how is receipt of the results acknowledged;
- what communication details need to be recorded;
- what escalation procedures are in place when communication is unsuccessful;
- how to assess performance and impact on patient outcome and safety?

Two paragraphs of the most commonly used accreditation standard, ISO 15189 indicate that "the laboratory shall have procedures for the immediate notification of a physician (or other clinical personnel responsible for patient care) when examination results for critical properties fall within established 'alert' or 'critical' intervals; and that the laboratory shall determine its critical properties and the 'alert'/'critical' intervals in agreement with the users of the laboratory" [8]. By definition, the ISO standards are usually brief and nonspecific and leave much room for interpretations. Some countries therefore developed explanatory notes or guidance documents to the ISO 15189 accreditation standard. Under the umbrella of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) we have surveyed 38 European countries in order to find out if they had any specific interpretations of the abovementioned two paragraphs in the standards. Out of 29 respondents (response rate 76%) only three countries, Hungary, Israel and the UK reported the availability of such additional guidance. It comes by no surprise then that national surveys run in various countries have shown significant inconsistencies and variations in alert thresholds defined by laboratories and in alert result notification practices [19–29]. Table 2 summarizes published survey findings of various management approaches and point to significant heterogeneity in practice both within and between countries [22–29].

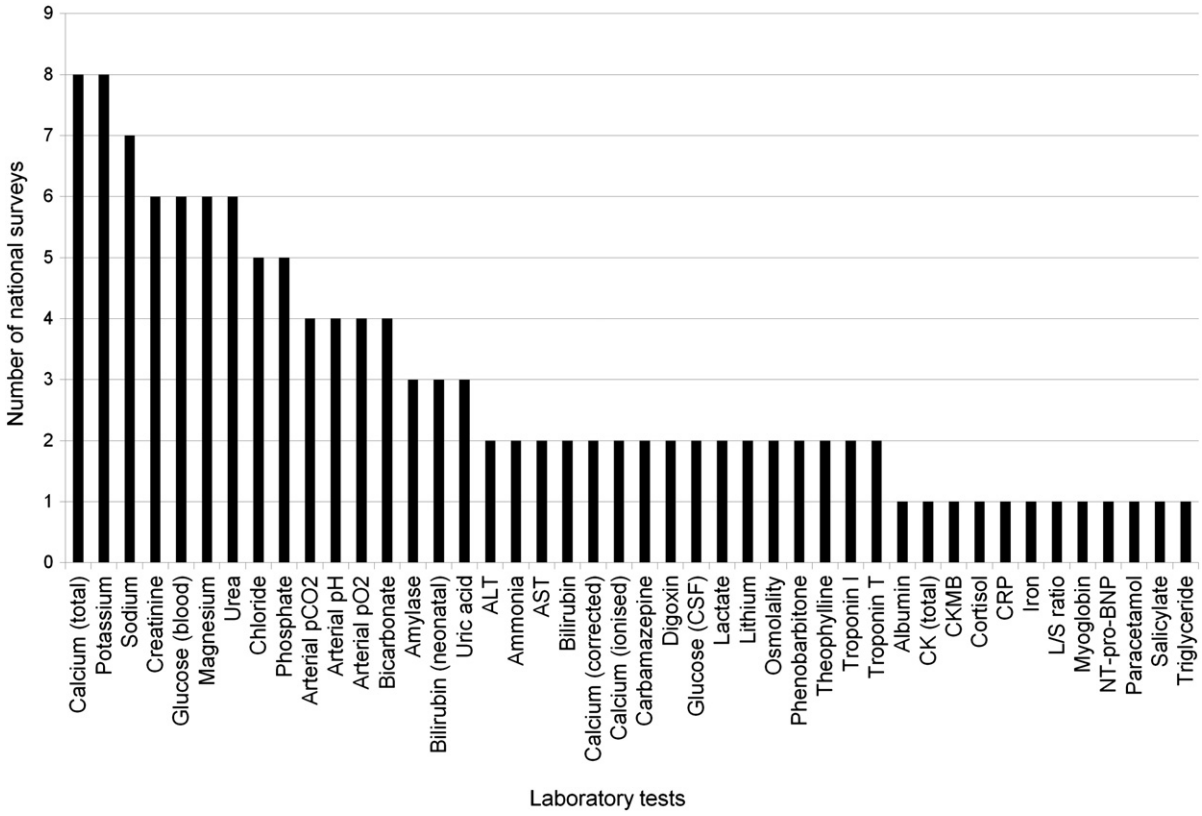

Fig. 1. Laboratory tests considered important in published surveys to be included in alert lists.

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004

Table 3
Most common biochemistry tests on adult alert lists in published surveys.

Laboratory test	US 2002 [22] (n = 623)	UK 2003 [19] (n = 87)		US 2007 [21] (n = 163)	Spain 2010 [26] (n = 36)		Australia 2012 [28] (n = 36)[a]	China 2013 [29] (n = 246[b], n = 599[c])		
		Phone to ward	Phone to doctor		Outpatients	Hospitalized		Emergency	Inpatients	Outpatients
Glucose (blood)	58%	62%	60%		72%	58%	100%	≈60%	≈90%	≈70%
Potassium	49%	63%	63%	99%	75%	58%	100%	≈65%	≈95%	≈70%
Sodium	43%	63%	63%	98%	75%	58%	97%	≈60%	≈90%	≈70%
Digoxin			44%				93%			
Lithium			40%	75%			92%			
Magnesium	9%	35%	30%	82%			88%			
Carbamazepine			26%				85%			
Phenytoin			35%				83%			
Amylase			39%		42%	22%	75%			
ALT					31%		73%			
Theophylline			24%				70%			
Bicarbonate	83%	17%	10%	84%			68%			
Creatinine	61%		28%	53%	61%	47%	67%	≈40%	≈60%	≈45%
Phenobarbitone			21%				67%			
Troponin T							67%	≈5%	≈10%	≈5%
Salicylate							65%			
Arterial pH	46%			56%			64%	≈70%	≈90%	≈65%
CK (total)							64%			
Phosphate	58%			64%	39%	25%	64%			
Calcium (corrected)		37%	37%				63%			
Calcium (total)	83%	33%	33%	98%	72%	58%	62%	≈60%	≈85%	≈65%
Paracetamol							62%			
Arterial pCO_2	45%			56%			58%	≈65%	≈80%	≈60%
Lactate	86%						54%			
Urea	86%		41%		58%	39%	53%	≈40%	≈60%	≈45%
Troponin I				49%			53%	≈20%	≈25%	≈20%
Arterial pO_2				56%			48%	≈65%	≈80%	≈60%
AST					33%		41%			
Ammonia	46%						41%			
Calcium (ionized)	17%						41%			
Glucose (CSF)	64%						30%			
CRP							29%			
Osmolality	86%						29%			
Triglyceride							29%			
Bilirubin				85%			25%			

Frequency (Australia 2012) = No. of laboratories that provided alert thresholds × 100% / No. of laboratories that perform that test.
Frequency (all other surveys) = No. of laboratories that provided alert thresholds × 100% / No. of laboratories that participated in survey.
n = number of laboratories participating in the survey.
≈: approximately equal to (NB: the Chinese survey did not provide raw data; therefore percentages could only be approximated from Figures).
[a] Out of 58 survey participants, 36 laboratories provided alert lists. Responses from laboratories within a large public or private pathology network, if they used the same alert list, were included only once.
[b] Blood gas questionnaires.
[c] Chemistry questionnaires.

3.1. Who should define alert lists?

Communication of critical and significantly abnormal results should represent a shared policy between the laboratory and medical care providers. In spite of the mentioned requirements in ISO 15189, in most countries laboratory professionals are still often the sole stakeholders in determining which tests and what alert thresholds should be on their list. Consultation with clinicians in compiling alert lists was shown to be more widespread in the United States (USA) [22]. Alert lists are often defined solely on empirical, anecdotal, and commercial basis, or based on guideline or other literature sources. For a selection of common tests, one third of laboratories surveyed in the USA used published literature as the primary source for their alert thresholds, while another third used non-laboratory medical staff recommendations [21]. An Italian national survey revealed that 57% of laboratories used data from the literature to compile their alert lists, 37% adopted the recommendations published by Italian laboratory medical societies [30], and 21% based their alert thresholds on opinions from clinicians at their institutions [25]. According to an Australian survey, resources used by laboratories to compile their alert lists include the laboratories' professional experience (62%), published literature (59%), international guidelines (41%), and consultation with doctors (41%) [28]. A survey conducted in Spain found that 52% of laboratories used their own data to establish their alert thresholds, 48% used the literature, and only 10% formed consensus with clinicians [26]. Similarly low clinical consultation rates (13%) were found in the most recently published Chinese survey [29]. Don-Wauchope and Chetty surveyed 115 physicians from two Canadian hospital corporations to assess the appropriateness of 11 alert thresholds in use by the laboratory. It was found that 7 thresholds did not meet the expected level of acceptance and thus required review [31]. This again highlights the importance of consultation with clinician groups when laboratories assemble their alert list.

3.2. What should be defined in alert lists?

A key area of debate and confusion is which laboratory tests should be included in alert lists and what alert thresholds should trigger notification. National surveys point to significant disparities (Fig. 1, Tables 3–5). Fig. 1 summarizes the frequency of tests for which published surveys collected alert threshold data, suggesting that these are the most likely tests that are expected to be included in most clinical biochemistry laboratories' lists. Table 3 shows the frequency of the most common biochemistry tests that laboratories reported in various surveys on adult alert thresholds. These data demonstrate the level of heterogeneity in judging which common biochemistry tests should be on the laboratory's alert list. Frequencies in Table 3 are not directly comparable

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004

Table 4
Range of lower alert thresholds of common biochemistry tests in published surveys.

Analyte	Units	US 2002 [22] Median (p10–p90)	UK 2003 [19] Mean (range)	US 2007 [21] Median (p5–p95)	Italy 2010 [25] Median (p5–p95)	Spain 2010 [26] Outpatients Median (p10–p90)	Thailand 2010 [27] Mean (±SD)	Australia 2012 [28] Median (range)	China 2013 [29] Median (p5–p95)
Sodium	mmol/L	120 (110–125)	122 (110–130)	–	120 (110–130)	120 (115–129)	121 (±7.3)	125 (120–130)	120 (110–125)
Potassium	mmol/L	2.8 (2.5–3.0)	2.7 (2.0–3.0)	2.9 (2.5–3.1)	2.8 (2.0–3.0)	2.8 (2.5–3.0)	2.6 (±0.4)	2.8 (2.2–3.0)	2.8 (2.5–3.0)
Bicarbonate	mmol/L	10 (10–15)	12 (5–18)	–	–	–	11 (±3.0)	15 (10–18)	–
Urea	mmol/L	–	–	–	–	–	4 (±5.7)	–	1.2 (0.2–2.0)
Creatinine	umol/L	–	–	–	–	–	16 (±8.8)	–	27 (10–43)
Glucose	mmol/L	2.20 (2.20–2.75)	2.4 (1.5–3.4)	–	–	2.50 (1.74–2.78)	2.58 (±0.48)	2.5 (1.5–3.0)	2.5 (2.1–3.0)
Calcium (total)	mmol/L	1.50 (1.50–1.75)	1.75 (1.5–2.0)	1.53 (1.50–1.78)	1.7 (1.4–2.1)	1.65 (1.50–1.86)	1.59 (±0.13)	1.78 (1.50–2.10)	1.60 (1.50–1.75)
Magnesium	mmol/L	0.49 (0.39–0.57)	0.48 (0.30–0.70)	0.40 (0.35–0.55)	0.50 (0.41–0.80)	–	0.46 (±0.22)	0.4 (0.2–0.6)	–
Phosphate	mmol/L	0.32 (0.32–0.65)	0.39 (0.30–0.60)	–	–	0.32 (0.32–0.57)	0.38 (±0.13)	0.4 (0.3–0.6)	–

Table 5
Range of upper alert thresholds of common biochemistry tests in published surveys.

Analyte	Units	US 2002 [22] Median (p10–p90)	UK 2003 [19] Mean (range)	US 2007 [21] Median (p5–p95)	Italy 2010 [25] Median (p5–p95)	Spain 2010 [26] Outpatients Median (p10–p90)	Thailand 2010 [27] Mean (±SD)	Australia 2012 [28] Median (range)	China 2013 [29] Median (p5–p95)
Sodium	mmol/L	160 (150–170)	154 (147–170)	–	160 (150–160)	160 (150–162)	158 (±11.3)	155 (150–160)	160 (150–170)
Potassium	mmol/L	6.2 (6.0–6.5)	6.1 (5.5–7.0)	6.0 (5.9–6.5)	6.2 (5.5–7.1)	6.3 (6.0–7.7)	6.4 (±1.0)	6.0 (5.4–6.9)	6.2 (5.8–7.0)
Bicarbonate	mmol/L	40 (40–45)	39 (35–50)	–	–	–	39 (±1.7)	40 (40–45)	–
Urea	mmol/L	29 (18–36)	26 (15–50)	–	–	61 (18–87)	31 (±13.3)	30 (12–45)	35.7 (20.0–37.8)
Creatinine	umol/L	442 (265–884)	419 (200–1800)	–	–	442 (264–654)	670 (±407)	300 (180–618)	650 (442–1000)
Glucose	mmol/L	24.8 (16.50–38.50)	21.8 (10–50)	–	–	22.2 (16.7–27.8)	23.9 (±5.8)	20.0 (8.0–30.0)	22.2 (15.0–30.0)
Calcium (total)	mmol/L	3.25 (3.00–3.50)	3.1 (2.8–3.5)	3.25 (3.00–3.50)	3.2 (2.7–3.5)	3.25 (2.96–3.50)	3.29 (±0.37)	3.00 (2.60–3.50)	3.50 (3.00–3.55)
Magnesium	mmol/L	1.91 (1.23–2.50)	1.83 (1.10–3.50)	2.05 (1.25–2.90)	2.00 (0.93–2.90)	–	2.11 (±0.53)	2.0 (1.4–4.0)	–
Phosphate	mmol/L	2.58 (1.78–3.23)	–	–	–	2.87 (1.95–2.91)	2.81 (±0.56)	3.0 (2.5–4.0)	–
Amylase	U/L	–	344 (70–1500)	–	–	375 (130–1000)	–	350 (90–1000)	–

p: percentile.

Table 6
Conditional alert lists.

Analyte	Units	Salt Lake City, USA [44]		Massachusetts, USA [15]			Royal College of Pathologists, UK [16]
		Low limit	High limit	Always phone within 1 h	Phone within 1 h first instance, and within 8 h thereafter	Phone within 8 h first instance only.	
Sodium	mmol/L	<120 (or fallen by >15 in previous 24 h and <130)	>155	<120 or >160			<120 or >150
Potassium	mmol/L	<2.7 (or fallen by >1.0 in previous 24 h and <3.2; or patient on digoxin and <3.3)	>6.0	<2.8 or >6.0			<2.5 or >6.5
Bicarbonate	mmol/L	<15: with urea > 50; <18: with urea < 50 or no urea ordered; <25: and bicarbonate fallen by ≥10 in 24 h		<10	10–15	>38	>30 (>10 if <16 yr)
Creatinine	umol/L					>354	>400 (>200 if <16 yr)
Glucose	mmol/L	<2.5	>27.8	<2.78 or >22.20			<2.5 or >25.0
Calcium (total)	mmol/L				<1.75 or >3.25		
Magnesium	mmol/L				<0.41 or >2.06		<0.4
Phosphate	mmol/L			<0.32			<0.3
Amylase	U/L					>500	5 × upper limit of normal

due to differing designs of each survey and whether they addressed hospital inpatient or general practice patient settings. Data from Spain illustrate that laboratories have differing policies for phoning critical results for inpatient wards, where such results are more expected, than for outpatient settings where critical results are less common and might need to trigger urgent referral to hospital [26]. Findings of the Chinese survey, however, highlight somewhat differing practices of more frequent notifications of hospital wards than outpatient clinics [29]. This may be explained by the difficulties in the logistics of managing critical outpatient communications, rather than by real clinical needs. These variations may be attributed, in part, to differences in the patient populations and clinical settings that laboratories serve, as well as differences in the test methodologies they employ [32]. However, the lack of published evidence-based clinical outcome data for all but a handful of laboratory medicine tests is probably the main contributor to the disparity in critical list composition between laboratories [22,31,33]. Irrespectively, one would imagine that at least certain tests, such as sodium, potassium, glucose, and calcium would be on all laboratories' alert list since these are parameters where we have fairly firm understanding of pathophysiology and some evidence from guidelines and outcome studies showing the association of analyte concentrations with critical pathological responses [17,34–36]. For example, while blood glucose is included in all Australian laboratories' alert list, in other countries it is only on the list in 60–70% of survey participants. Similarly, except for Australia and the USA, only 60–75% of surveyed laboratories in other countries seem too provide alert thresholds and notification protocols for potassium.

Critical tests that are always reported regardless of the result are rarely defined and most national surveys have not addressed this question in sufficient detail to draw meaningful conclusions. In many institutions, alert lists are extended to include significantly abnormal or medically important results that are not particularly time sensitive [33,37]. Some authors recommend more *customized approaches* whereby laboratory professionals review and assess the need for notifying alert results based on requester characteristics, patient location, medical history, previous results, laboratory result patterns, reflex testing algorithms, etc. [17,38–40]. Alert lists that are too inclusive can greatly increase the number of telephone calls, which desensitizes medical staff to truly critical results requiring immediate action as well as placing unnecessary burden on laboratory staff [15,32,37]. On the other hand, lists that are too exclusive (or have thresholds that are too high or low) may lead to life threatening situations not being attended to [32,37].

Another area of contention is the selection of *alert thresholds*. The guiding principle for deciding alert thresholds should be that they represent clinical decision thresholds that trigger appropriate actions in order to prevent harm and improve patient outcomes [28]. Tables 4 and 5 show the adult median and range of the lower and upper alert thresholds for critical results of commonly used tests reported in surveys. While median values show fairly good agreement across the globe, the range of results in those surveys highlights sometimes substantial variations between laboratories. Alert lists can become quite complex and may include differing thresholds for critical and significantly abnormal results. Age, sex or other patient characteristics related to the condition or treatment, case mix and healthcare settings may also influence the selection of thresholds for notification.

Extensive data from various US national surveys reveals that adult and children's hospitals chose different alert threshold levels [41]. A comparison of the thresholds used for urea, creatinine, platelets and prothrombin time suggests that children's hospitals are more conservative in their surveillance of renal and hemostasis problems. However, non-specialized hospital laboratories rarely use age related alert thresholds with the exception of newborns, where the first 28 days of life sees dramatic and rapid physiological changes in the respiratory, cardiovascular, hepatic, hematological and renal systems [41,42]. A US survey revealed that 67% of laboratories used unique thresholds for populations distinguished by age, 16% for health care setting, and 10% for disease type. No laboratories reported unique thresholds for ethnicity [21]. In the Australian survey, 97% and 81% of laboratories have thresholds for critical and significantly abnormal results, respectively. Some laboratories reported different policies for outpatients (21%), tests performed out-of-hours (27%), physicians external to their institution (8%), and tests performed on behalf of referral laboratories (4%) [28]. The Royal College of Pathologists in the UK has issued a master list of alert thresholds for out of hours reporting to general practitioners in which it also used some age-dependent thresholds (Table 6) [16].

As highlighted in the definitions section, rapid changes in laboratory results might also indicate life threatening situations, which could go unattended if critical result reporting is performed solely on the basis of critical limits. For instance, overzealous correction of hyponatremia can cause central pontine myelinolysis, an irreversible neurological condition with grave consequences for patients [43]. Thus alert lists should contain rules to help laboratory staff identify significant changes in results that need clinical notification. Previous research based on patient's laboratory results at a hospital in Salt Lake City identified 60 potentially life-threatening conditions. Due to their medical implications and relative high frequency, a subset of these conditions was selected and evaluated by six experts in surgery, cardiology, internal medicine and critical care. Criteria for alerting to these situations, including dangerously rapid changes in test results (Table 6), were programmed into an electronic laboratory alert system [44].

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004

Policies and practices are inconsistent about the needs for communicating *repeatedly critical results*. The Joint Commission (a health care organization accrediting body in the USA) allows critical results to be defined differently for patients with a particular diagnosis and for repeat tests [45]. There is disparity in various surveys in repeated communication of critical results, once the laboratory has notified the first occurrence of such results (Table 2). More laboratories in Australia seem to have policies of not reporting subsequent critical results than in any other country surveys [28]. As mentioned earlier, laboratories should try to limit the frequency of repeat calls to avoid alert fatigue and unnecessary distraction of clinical staff. The Massachusetts consensus group also recommended that laboratories reduce the number of notifications where the patient's condition is known by considering the amount, timeframe and direction in which the result has changed as well as the medical history of the patient [15]. A recent retrospective study in a large tertiary hospital in China investigated the relationship between the frequency of repeat critical results for potassium and platelet count and clinical outcomes. This study found that increased frequencies of repeat critical results were associated with longer hospital stay and increased mortality rate [46]. Therefore, laboratories are advised to design repeat alert result policies and include not only critical and non-critical tests and their thresholds on their alert list but also instructions for the frequency of notification of repeat alert results. Policies on repeated communications should be developed only after careful risk analysis and in agreement with clinicians to ensure that they have appropriate procedures in place at their level for handover of information to shift staff and for careful monitoring and treatment of patients in persistently critical conditions [32,46].

3.3. How alert results are verified?

Re-testing to verify critical results before reporting is still quite common practice, although with lesser frequency in the USA (Table 2) [23]. Most of these verification practices date back to times when laboratories used less sophisticated automated systems. Recent studies have shown that repeating measurements add little to the safety of patients. Analytical error rates by repeat testing are only in the range of 2–3%, but repeat verifications have been shown to delay rapid release of critical results which calls for a reconsideration of such practices [47,48].

3.4. What is the timeframe of communication?

A critical result communication consensus group in Massachusetts Hospitals recommended that alert lists are segmented into three levels of urgency: a red zone where the patient is in imminent danger of death unless treated immediately, with results to be notified within 1 h; an orange zone where prompt clinical attention is required to avoid serious adverse outcomes, with results to be notified within 6 to 8 h; and a yellow zone where serious adverse consequences may occur without treatment in a timely and reliable manner, with results to be notified within 3 days [15]. This segmentation allows laboratory staff to quickly and efficiently deliver urgent red zone results to the clinicians (as long as the red zone tests are kept to a small number), and later deal with delivery of the less urgent results (that may otherwise slip through the cracks). According to survey findings in Table 2, the timeframe within which alert results need to be communicated is defined in approximately half of the laboratories only which suggests that most laboratories do not have such prioritization of alert results and even when critical results are notified there might be significant delays. Delayed communication and the lack of appropriate monitoring of the effectiveness of critical result notification procedures were also highlighted in the previously mentioned WHO, National Quality Forum and the Clinical Excellence Commission reports [1,3,4].

3.5. What communication channels are used for delivering alert results?

In spite of the wide-spread use of electronic patient records and laboratory information systems, national surveys reveal that most countries still use traditional telephone communications for delivering critical results (Table 2). However, there is an increasing interest in automated alternatives. A 12-month study in an Italian teaching hospital revealed that the average time for acknowledged computerized critical result notification (SMS to referring physician plus video alert to ordering clinician) was 11 min compared to 30 min for verbal notification by telephone [49]. A 1000 bed academic medical center in Nashville Tennessee introduced an electronic ALERTS system using alphanumeric pagers which eliminated approximately 9000 phone calls a year for laboratory technologists, with a small number of phone calls required for telephone operators where pagers were not acknowledged within 10 min [50]. A recent meta-analysis has shown that call centers deliver critical results more efficiently than laboratory personnel [51]. Survey summaries however indicate that such dedicated facilities are rarely accessible to laboratories in most countries (Table 2). The current state of information technology in most hospitals is still too rudimentary to allow the implementation of electronic notification systems with automated feed-back on receiving alert results. Using call centers in a carefully designed notification system is therefore still considered a more viable option than automated e-alerts, which in the longer run, however, are expected to gain more widespread use [28].

3.6. Who should deliver and receive alert results?

In the majority of national surveys mostly laboratory technicians report critical results except in Italy where predominantly laboratory managers, or medically qualified laboratory staff are involved in such communications [25]. The Clinical Laboratory Improvement Amendments of 1988 (CLIA), of which all United States laboratories must adhere to in order to access Medicare payments, requires laboratories to immediately alert the individual requesting the test (and if applicable the individual responsible for using the test) when the test result indicates an imminently life-threatening condition [52]. In practice, attempting to contact a physician can be an arduous and time-consuming task. In a US survey, 75% of respondent laboratories believed that outpatient physicians, not returning calls or pagers, was the greatest obstacle to critical result reporting success [24]. In an Italian survey, 56% of respondent laboratories considered that the major challenge in their critical result notification process was reporting the result to the actual physician assigned to the patient [25]. The ISO 15189 accreditation standard and the College of American Pathologists laboratory accreditation inspection checklist deem clinical personnel responsible for patient care (i.e. physicians or nurses) as suitable recipients of critical results [8,10]. According to our survey summary, most laboratories deliver alert results to doctors and nurses and this practice seems fairly homogeneous across countries, except for Spain and China where nurses are much less or not at all involved in such communications (Table 2).

3.7. How is receipt of the results acknowledged?

Read-back of verbal communications of results is a varied practice across countries (Table 2), even though inappropriate recording of results is a major potential patient safety hazard. Even when alert results are communicated electronically, some form of acknowledgement system must be put in place. However, receiving acknowledgement of receipt of a critical result from a clinician should not automatically lead to the assumption that timely follow-up will occur. A study conducted at the Veterans Affairs Medical Centre in Texas found that for critical alerts not followed up clinically within 30 days, there was no significant difference between the number of alerts that were acknowledged (within the view alert window of the electronic medical record screen) and the number of alerts that went unacknowledged [53].

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004

Table 7
National guidelines for managing critical laboratory results in Europe.

Country	Authority/organization	Nature of guidance document	Method/source	Web address (*last accessed 30 August 2013*)
Croatia	Croatian Chamber of Medical Biochemists	Alert list of laboratory tests and thresholds for communicating critical results	Alert thresholds adapted from literature are provided as guidance to laboratory professionals	www.hkmb.hr/povjerenstva/strucna-pitanja.html
Italy	Intersocietary working group SIBioC-SIMeL-CISMEL	Best practice guideline with starter set for alert list and thresholds for communicating critical results which laboratories may adapt in consultation with their clinical users	Officially published consensus guideline for laboratory professionals [30]	http://www.sibioc.it/upload/bc/32/3/lippi.pdf http://www.simel.it/it/riviste/articolo.php/2349
Poland	Polish Society of Laboratory Diagnostics (PTDL)	Best practice guideline with starter set for alert list and thresholds for communicating critical results which laboratories may adapt in consultation with their clinical users	Expert opinion and literature-based document open to broad public commenting by laboratory specialists in form of a professional web-based blog	http://www.krytyczne.blogspot.com/ http://www.ptdl.pl/download/Wartosci_krytyczne.pdf
UK	Royal College of Pathologists	Guidelines for out of hours reporting of critical results to primary care physicians	Officially published consensus guideline [16]	http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/g025_outofhoursreporting_nov10.pdf

3.8. What communication details need to be recorded?

It is a requirement of the ISO 15189 accreditation standard (Subclause 5.8.10) that records are maintained of actions in response to critical results, with difficulties in meeting these requirements also recorded and reviewed during audits [8]. Keeping records of alert result communications enables laboratories to monitor their performance in delivering such results and thus identify improvements for their management procedures. Ideally, records should be stored electronically within a database to allow for statistical analysis of the data. Information collected within the record should include:

- the identity of the individual who delivered the result,
- the date and time that the communication was made,
- the identity of the recipient of the result,
- the location of the recipient of the result (e.g. hospital ward, general practice, outpatient clinic)
- the identity of the patient tested,
- the type of sample tested,
- the date and time that the sample was collected,
- the test that was performed, and
- the test result with the unit of measure.

Recording other relevant factors, such as difficulties encountered in result delivery or whether acknowledgement of receipt was obtained, provides useful information for auditors of the communication process.

3.9. What escalation procedures are in place when communication is unsuccessful?

Locating an alternate caregiver who can take responsibility for following up an alert result can be a time consuming task. Laboratories should implement a step by step procedure to direct staff in identifying the most appropriate person to receive an alert result when the requesting doctor is unavailable. A flow chart published by Singh and Vij is a good example of an escalation procedure for notifying alert results [13]. In that procedure, laboratory staff attempts to contact the primary care physician if the ordering doctor is not available. Failing that, staff should attempt to contact the primary care physician's supervisor, Chief of Service, then the Medical Center director. Designing similar escalation procedures depends on local circumstances and the levels of authority medical teams are willing to delegate to other health care staff that can responsibly action alert result notifications from the laboratory. While this is certainly not an area for harmonization, it is advised that laboratories develop escalation procedures in agreement with their clinical users.

3.10. How to assess performance and impact on patient outcome and safety?

Performance in the delivery and receipt of critical results should be monitored to check for compliance and to identify areas where procedures can be improved [13,19,30]. Useful performance indicators for measuring laboratory staff compliance to alert result notification procedures include: i) the percentage of alert results requiring communication that were communicated, ii) the average time taken to communicate an alert result (from the time the result was first available), and iii) the percentage of communicated alert results for which acknowledgement was received [10,54]. Alert result notification is a service the laboratory offers to clinicians to ensure that patients receive urgent medical treatment when they need it. The effectiveness of this service can and should be measured both from the process and clinical outcome point of view. Parameters of the process that could be improved by monitoring and review include the appropriateness of the chosen alert thresholds, setting timeframes in which various types of alert results should be communicated, determining who is best to receive the result, and identifying the most effective means of communication. The best way to assess the clinical outcome of the alert result management system is to monitor the actions taken and the health outcomes of the patients when such results are delivered.

4. Guidelines to facilitate harmonization of practices

The abovementioned variations in procedures and what tests and thresholds are included in the alert lists of laboratories call for more clear guidance and at least some degree of harmonization of best practice for communicating critical and significantly abnormal results. The practice variations explored in a number of surveys and the lack of specific guidance available for laboratories to design their alert result management policies have led to the appearance of a number of safe practice recommendations in the literature [13,15,16,30]. Information from 29 European countries who responded to our survey has revealed that 4 countries (Croatia, Italy, Poland and the UK) had some form of officially endorsed national guideline and/or alert list in 2012 (Table 7). Acknowledging the importance of harmonization for patient safety, in Australia the Royal College of Pathologists and the Australasian Association of Clinical Biochemists have formed a working party assigned to identify gaps in current laboratory practices and produce national guidance for managing alert results. This group is also working on the provision of a "starter" set of alert thresholds that individual laboratories can discuss with their local clinicians and tailor to meet their clinical needs. The Clinical and Laboratory Standards Institute is currently preparing an international guideline which is expected to provide comprehensive guidance and help harmonize critical result management procedures across

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004

various pathology disciplines worldwide. Global harmonization of management procedures in this field is expected to ensure that all laboratories will better contribute to patient safety, and to enable benchmarking of performance that is expected to improve service quality in the post–post-analytical phase of laboratory processes.

While national and international guidelines aim at standardizing practice, it must be acknowledged that the "one size fits all" mentality in communicating alert results would most likely fail. Therefore guidelines should remain reasonably flexible to facilitate customized adoption and adherence where local specifics influence the feasibility and implementability of recommended procedures. Guidelines should aim at harmonization of practices where patient safety is at highest risk and in such areas recommendations should be more prescriptive. For example, some differences in practices, such as who notifies alert results to whom and by what mode of transmission, or how repeatedly critical results are communicated are easily explainable with and much influenced by local, educational, organizational, legal and cultural circumstances. Other shortcomings, such as not involving clinicians in the design of the alert list and procedure, not defining the timeframes of reporting, not having agreed escalation processes when results cannot be delivered within predefined timescales, or lack of read-back and recording of verbally communicated results, are less easy to explain and accept for patient safety reasons.

5. Methods to facilitate harmonization of alert lists

Laboratories all around the world face difficulties when designing alert lists, as there is no agreement on what is deemed critical and a medical emergency. How should laboratories and clinicians decide what tests and what alert thresholds should be on their alert list? The answer to this question best starts with identifying an individual institution's and most importantly patients' needs and requirements.

5.1. How to decide which tests to include in alert list?

Laboratories should extensively consult with their clinical users to find out what tests they consider critical and what treatment protocols or referral pathways they have to manage alert results. As mentioned in the very beginning of this article, there is very little benefit in testing and designing systems for urgent notification of critical or significantly abnormal results, if such laboratory interventions do not fit into any clinical pathway or are not followed by appropriate medical action. Hospital incident records of unexpected fatalities and 'near miss' cases, root-cause analysis reports and findings from risk assessments and patient safety audits could inform such decisions. Review of the typical case mix and subspecialties of health care organizations to which the laboratory provides its services can also guide decisions. Review of well-described pathophysiological associations with certain biomarkers and test results as well as engaging clinical pharmacologists, toxicologists and infection control committees would grossly help in designing more relevant and up-to-date alert lists. The benefit of involving various stakeholders in the planning or updates of alert lists is that these consultations help in implementing a shared policy for alert result notification. Our summary of multinational surveys presented in Table 3 and Fig. 1 may also help in deciding which biochemistry tests should be on one's alert list. A larger multinational survey that has been recently conducted by the task force group of EFLM may shed even more light on the current state-of-the-art in Europe — so watch this space.

5.2. How to decide which thresholds to include in alert list?

There are currently no criteria for laboratories to refer to in setting alert thresholds. As discussed earlier, alert thresholds should grossly impact medical decisions and therefore we consider them as clinical decision limits. In this context they represent "the threshold above which there is significant morbidity and mortality and above which treatment has been shown to significantly improve these patient-centered outcomes — 'significant' meaning important to people's quality of life or lifespan, rather than statistical significance" (personal communication by Professor Les Irwig, University of Sydney).

Currently used alert thresholds, including the majority which has been published in the literature, are typically based on consensus and personal observations from clinicians and pathologists. Often laboratories do not even have information on the exact source of their alert thresholds as often these are inherited or had gone through a number of modifications over years. Before describing the conceptual framework and approaches for establishing alert thresholds, we would like to emphasize that the minimum requirement from laboratories is that they explicitly refer to the source of their alert thresholds and record any consultations and reasoning that justify the selection of those limits. These records are not only important for traceability but they may also be called upon in legal cases. It would be also desirable that apart from the source, the quality of the information behind the alert thresholds is explicitly stated so that laboratories and clinicians are aware of the strengths (or weaknesses) of the evidence behind the data. This potentially has an influence on medical decisions, especially when recommended alert thresholds are locally modified and adapted.

A hierarchical model for setting analytical quality specifications was created by an international consensus in Stockholm in 1999 [55]. Sikaris has proposed that a similar concept could be designed for ranking the quality of candidate reference intervals (i.e., healthy result ranges for laboratory tests) and clinical decision limits (i.e., test result thresholds beyond which clinical decisions are made for diagnosis or various treatment options) [56]. Since alert thresholds are like clinical decision limits, we hypothesize that this modified version of the Stockholm hierarchy would be suitable for classifying the sources of alert thresholds and thus could assist in designing alert lists in a more evidence-based and transparent manner. According to Sikaris' concept, the quality of clinical decision limits can be ranked and based on different levels of evidence:

- Level 1: clinical outcomes in specific clinical settings
- Level 2: consultation with clinicians in local settings
- Level 3: published professional recommendations of national or international expert bodies
- Level 4: national or international surveys of current practice (i.e. the 'state-of-the-art')
- Level 5: individual publications, textbooks, expert opinion.

Ideally, alert thresholds should be based on well-designed and conducted clinical outcome studies (Level 1). If high quality outcome studies were available for many tests, laboratory professionals could approach their clinician clients with a more objective and evidence-based "starter set" of proposed alert thresholds for further consultation and endorsement. In our view where reasonable quality outcome data exist for a specific patient population, alert thresholds could and should be harmonized. It is important to highlight the importance of appropriate translation of such evidence to local practice. Laboratory professionals therefore must scrutinize and critically appraise such evidence by asking the following questions:

- Is this outcome study relevant to my patient population and setting?

Consider prevalence of condition, heath care setting, patient demographics, comparability of clinical pathways, availability of adequate treatment and further diagnostic options, etc. If the answer to these questions is no, then the rest of the below questions should not even be addressed.

- Is this outcome study well designed and conducted?
- What patient-centered outcomes did this study investigate and are they relevant to my setting?
- Does this study use laboratory assays for measurement which has comparable analytical performance to my assay?
- Are the diagnostic or alert thresholds comparable to my assay?

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004

Are clinical performance characteristics (i.e. diagnostic or prognostic accuracy) of the published assay comparable to my assay? (e.g. the diagnostic accuracy of 4th generation and 'high-sensitivity' Troponin assays are quite different).

In the lack of suitable outcome data, the best practice that is also recommended in existing standards and guidelines is to form a consensus with clinicians on the best course of action, as described earlier (Level 2). Published recommendations of professional organizations, such as those mentioned earlier (Table 7) and which are available in some countries represent Level 3 in this hierarchy [13,15,16,30]. In this review, for selected tests, we have also collected all available alert threshold data from multinational surveys which illustrate current practice (Level 4). The problem is that such surveys represent very different health care settings and populations. Furthermore, surveys have revealed that most laboratories use thresholds or their modifications published by single experts or in textbooks many decades ago (i.e. Level 5 evidence) and summary data from global surveys simply reflect that practice and evidence level. Thus according to the current state of affairs Level 4 evidence is probably not any better than Level 5 on the above hierarchy. Therefore it is not unreasonable to presume that the "state-of-the-art" is already distorted and it is neither transparent where the information came from nor is it based on any evidence or clinical observation which would link alert thresholds to pathophysiologic changes or adverse patient events.

Alert result notification must be a shared policy and responsibility of laboratory and clinical staff. Harmonization of some practices is necessary, but cannot be achieved for all aspects of alert result communications. Laboratory professionals should be engaged more proactively in clinical consultations about the needs of clinicians and patients and should be measuring quality indicators and perform clinical audits to monitor the clinical and cost-effectiveness of their alert communication system. The information gathered this way will help refine alert lists and communication policies and will contribute to safer and higher quality patient care.

Acknowledgments

The authors wish to thank members of the Critical Results Harmonisation Working Party of the Australasian Association of Clinical Biochemists, and the Critical Results Task and Finish Group of the European Federation of Clinical Chemistry and Laboratory Medicine for collaborative work that contributed to many of the concepts described in this review. We also thank the assistance of Silvia Cattaneo at EFLM office who coordinated the collection of information presented here from European countries.

References

[1] The Research Priority Setting Working Group of the World Alliance for Patient Safety. Summary of the evidence on patient safety: implications for research. Geneva: World Health Organization; 2008 136 [http://www.who.int/patientsafety/information_centre/20080523_Summary_of_the_evidence_on_patient_safety.pdf, (last accessed 1 September 2013)].
[2] Callen J, Georgiou A, Li J, Westbrook JI. The safety implications of missed test results for hospitalised patients: a systematic review. BMJ Qual Saf 2011;20:194–9.
[3] National Quality Forum (NQF). Serious reportable events in healthcare—2011 update: a consensus report. Washington DC: NQF; 2011 [http://www.qualityforum.org/Publications/2011/12/Serious_Reportable_Events_in_Healthcare_2011.aspx (last accessed 1 September 2013)].
[4] Clinical Excellence Commission Patient Safety Team. Clinical focus report: diagnostic tests — how access and follow-up affect patient outcomes; September 2011 [http://www.cec.health.nsw.gov.au/__documents/programs/patient-safety/patient-safety-report-diagnostic-tests.pdf (last accessed 1 September 2013)].
[5] Walz SE, Darcy TP. Patient safety and post-analytical error. Clin Lab Med 2013;33(1):183–94.
[6] Lundberg GD. When to panic over abnormal values. MLO Med Lab Obs 1972;4:47–54.
[7] Critical values — more than 3 decades of experience: an expert interview with George D. Lundberg, MD. Medscape; Sep 05, 2007 [http://www.medscape.com/viewarticle/560353 (last accessed 1 September 2013)].
[8] International Organization for Standardization. ISO 15189:2009: medical laboratories — particular requirements for quality and competence. Geneva, Switzerland: ISO; 2009.
[9] The Joint Commission. National Patient Safety Goals, Laboratory Accreditation Program; 2013 [http://www.jointcommission.org/assets/1/18/NPSG_Chapter_Jan2013_LAB.pdf (last accessed 1 September 2013)].
[10] College of American Pathologists, Commission on Laboratory Accreditation, Laboratory Accreditation Program. Laboratory general checklist — questions related to reporting of results only. GEN.41320-41340 http://www.cap.org/apps/docs/pathology_reporting/LabGeneralChecklist_Reporting.pdf; 2005 . [last accessed 1 September 2013].
[11] Standards for Medical Laboratories. Clinical Pathology Accreditation Ltd, UK; Version 2.02; November 2010 [http://www.cpa-uk.co.uk/files/PD-LAB-Standards_v2.02_Nov_2010.pdf (last accessed 1 September 2013)].
[12] Lundberg GD. It is time to extend the laboratory critical (panic) value system to include vital values. MedGenMed 2007;9(1):20 [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1925001/ (last accessed 1 September 2013)].
[13] Singh H, Vij MS. Eight recommendations for policies for communicating abnormal test results. Jt Comm J Qual Patient Saf 2010;36(5):226–32.
[14] VHA Directive 2009–019. Ordering and reporting test results. Veterans Health Administration; Mar 24, 2009 [http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=1864 (last accessed 1 September 2013)].
[15] Hanna D, Griswold P, Leape LL, Bates DW. Communicating critical test results: safe practice recommendations. Jt Comm J Qual Patient Saf 2005;31(2):68–80.
[16] The Royal College of Pathologists (UK). Out-of-hours reporting of laboratory results requiring urgent clinical action to primary care: advice to pathologists and those that work in laboratory medicine. London, UK: RCPath; 2010.
[17] Kost G, Hale KN. Global trends in critical values practices and their harmonization. Clin Chem Lab Med 2011;49(2):167–76.
[18] Kost GJ. Critical limits for urgent clinician notification at US medical centers. JAMA 1990;263(5):704–7.
[19] Tillman J, Barth JH. A survey of laboratory 'critical (alert) limits' in the UK. Ann Clin Biochem 2003;40(Pt. 2):181–4.
[20] Lippi G, Giavarina D, Montagnana M, Luca Salvagno G, Cappelletti P, Plebani M, et al. National survey on critical values reporting in a cohort of Italian laboratories. Clin Chem Lab Med 2007;45(10):1411–3.
[21] Wagar EA, Friedberg RC, Souers R, Stankovic AK. Critical values comparison: a College of American Pathologists Q-Probes Survey of 163 clinical laboratories. Arch Pathol Lab Med 2007;131(12):1769–75.
[22] Howanitz PJ, Steindel SJ, Heard NV. Laboratory critical values policies and procedures: a College of American Pathologists Q-Probes Study in 623 institutions. Arch Pathol Lab Med 2002;126(6):663–9.
[23] Valenstein PN, Wagar EA, Stankovic AK, Walsh MK, Schneider F. Notification of critical results: a College of American Pathologists Q-Probes study of 121 institutions. Arch Pathol Lab Med 2008;132(12):1862–7.
[24] Dighe AS, Jones JB, Parham S, Lewandrowski KB. Survey of critical value reporting and reduction of false-positive critical value results. Arch Pathol Lab Med 2008;132(10):1666–71.
[25] Piva E, Sciacovelli L, Laposata M, Plebani M. Assessment of critical values policies in Italian institutions: comparison with the US situation. Clin Chem Lab Med 2010;48(4):461–8.
[26] Llopis Diaz MA, Gomez Rioja R, Alvarez Funes V, Martinez Bru C, Cortes Rius M, Barba Meseguer N, et al. Critical values reporting: Results of a Spanish laboratories survey. [Spanish] Revista del Laboratorio Clinico 2010;3:177–82.
[27] Sirisali K, Manochiopinij S, Leelahakul P, Ruengrai V, Sattayakom A, Sirisali S. Critical value of the clinical laboratory test in Thailand. J Med Assoc Thai 2010;93(Suppl. 6):S22–7.
[28] Campbell C, Horvath A. Towards harmonisation of critical laboratory result management — review of the literature and survey of Australasian practices. Clin Biochem Rev 2012;33(4):149–60.
[29] Zeng R, Wang W, Wang Z. National survey on critical values notification of 599 institutions in China. Clin Chem Lab Med 2013:1–9.
[30] Lippi G, Caputo M, Banfi G, Buttarello M, Ceriotti F, Daves M, et al. For the Intersociety Working Group SIBioC-SIMeL-CISMEL on extra-analytical variability of laboratory data. Recommendations for the detection and management of critical values in clinical laboratories [Italian]. Biochim Clin 2008;32:209–16 [and RIMeL/IJLaM 2008;4;28–35].
[31] Don-Wauchope AC, Chetty VT. Laboratory defined critical value limits: how do hospital physicians perceive laboratory based critical values? Clin Biochem 2009;42(9):766–70.
[32] Genzen JR, Tormey CA. Pathology consultation on reporting of critical values. Am J Clin Pathol 2011;135(4):505–13.
[33] Valenstein P. Critical communication. Clin Chem 2010;56(3):334–5.
[34] Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, et al. Special report. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2011;57(6):e1-47 [(http://www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/diabetes_update/Pages/default.aspx) (last accessed 1 September 2013)].
[35] Howanitz JH, Howanitz PJ. Evaluation of total serum calcium critical values. Arch Pathol Lab Med 2006;130(6):828–30.
[36] Howanitz JH, Howanitz PJ. Evaluation of serum and whole blood sodium critical values. Am J Clin Pathol 2007;127(1):56–9.
[37] American Association for Clinical Chemistry. Critical results: is your lab's definition crisp or muddled? http://www.aacc.org/members/nacb/NACBBlog/Lists/Posts/Post.aspx?ID=68# . [last accessed 1 September 2013].
[38] Lum G. Critical limits (alert values) for physician notification: universal or medical center specific limits? Ann Clin Lab Sci 1998;28(5):261–71.
[39] Barron J, Ng C, Aspin L, Robinson L-J, Smith G. Reflex testing to define action limits for community-based requests. Ann Clin Biochem 2012;49(Pt 4):337–40.

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004

[40] Salinas M, López-Garrigós M, Gutiérrez M, Lugo J, Flors L, Leiva-Salinas C. Should we customise critical value procedure according to patient origin and laboratory turnaround time? J Clin Pathol 2013;66(4):269–72.
[41] Kost GJ. Using critical limits to improve patient outcome. MLO Med Lab Obs 1993;25(3):22–7.
[42] Sharma A, Ford S, Calvert J. Adaptation for life: a review of neonatal physiology. Anaesth Intensive Care Med 2010;12(3):85–90.
[43] Chakraborty S, Bhattacharya C, Das S, Sen S. Delta check: a must in the management of hyponatremia. Clin Chem Lab Med 2013;51(7):e161–2.
[44] Tate KE, Gardner RM, Weaver LK. A computerized laboratory alerting system. MD Comput 1990;7(5):296–301.
[45] The Joint Commission. Standards FAQ details — critical tests, results and values — NPSG. Goal 2. 02.03.01: chronically critical values and repeatedly critical values. Revised November 24, 2008 http://www.jointcommission.org/mobile/standards_information/jcfaqdetails.aspx?StandardsFAQId=394&StandardsFAQChapterId=77 [last accessed on 1 September 2013].
[46] Yang D, Zhou Y, Yang C. Analysis of laboratory repeat critical values at a large tertiary teaching hospital in China. PLoS One 2013;8(3):e59518. http://dx.doi.org/10.1371/journal.pone.0059518.
[47] Toll AD, Liu JM, Gulati G, Behling EM, Kocher WD. Does routine repeat testing of critical values offer any advantage over single testing? Arch Pathol Lab Med 2011;135(4):440–4.
[48] Deetz CO, Nolan DK, Scott MG. An examination of the usefulness of repeat testing practices in a large hospital clinical chemistry laboratory. Am J Clin Pathol 2012;137(1):20–5.
[49] Piva E, Sciacovelli L, Zaninotto M, Laposata M, Plebani M. Evaluation of effectiveness of a computerized notification system for reporting critical values. Am J Clin Pathol 2009;131(3):432–41.
[50] Parl FF, O'Leary MF, Kaiser AB, Paulett JM, Statnikova K, Shultz EK. Implementation of a closed-loop reporting system for critical values and clinical communication in compliance with goals of the joint commission. Clin Chem 2010;56(3):417–23.
[51] Liebow EB, Drezon JH, Fontanesi J, Favoretto AM, Baetz RA, Shaw C, et al. Effectiveness of automated notification and customer service call centers for timely and accurate reporting of critical values: a laboratory medicine best practices systematic review and meta-analysis. Clin Biochem 2012;45(13–14):979–87.
[52] Medicare Medicaid, Programs CLIA. Laboratory requirements relating to quality systems and certain personnel qualifications. Fed Regist 2003;68:3639–714.
[53] Singh H, Thomas EJ, Sittig DF, Wilson L, Espadas D, Khan MM, et al. Notification of abnormal lab test results in an electronic medical record: do any safety concerns remain? Am J Med 2010;123(3):238–44.
[54] Sciacovelli L, O'Kane M, Skaik YA, Caciagli P, Pellegrini C, Rin GD, et al. Quality indicators in laboratory medicine: from theory to practice. Clin Chem Lab Med 2011;49:835–44.
[55] Kenny D, Fraser CG, Hyltoft Petersen P, Kallner A. Strategies to set global analytical quality specifications in laboratory medicine — consensus agreement. Scand J Clin Lab Invest 1999;59:585.
[56] Sikaris K. Application of the Stockholm hierarchy to defining the quality of reference intervals and clinical decision limits. Clin Biochem Rev 2012;33(4):141–8.

Please cite this article as: Campbell CA, Horvath AR, Harmonization of critical result management in laboratory medicine, Clin Chim Acta (2013), http://dx.doi.org/10.1016/j.cca.2013.11.004