BIOMED 2 - SUBPROJECT 8
REPORT SUMMARISING ACHIEVEMENTS AND FINAL RECOMMENDATIONS

The content of this report is based on a meeting held at CHUV, Lausanne, Switzerland, March, 7th, 2000.
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This subproject served to summarise objectively achievements of Biomed 2 and to produce recommendations for future developments in European-wide quality assurance of laboratory measurements in relation to inherited metabolic disorders.

Introduction

Quality control in diagnosis and monitoring of rare inherited disorders of metabolism must be performed at the international level due to the small number of laboratories in any single country. Major strides have been made in the establishment of QC schemes at the European level through the activities of ERNDIM, initiated and expanded with the support of a Biomed I grant (1994, BMHI-CT94-1074).
By 1998 significant progress was evident with participation of 201 laboratories from 30 countries, 22 European, in various schemes for quantitative amino acids, qualitative organic acids, quantitative organic acids, special assays and one proficiency testing scheme for the Netherlands/Germany/Belgium. Furthermore important improvements in performance of participating laboratories was documented.

In spite of these advances there was clearly need for further improvements in the level of performance of participating laboratories, in increasing the availability of schemes, and for wider participation of IEM laboratories in ERNDIM schemes.
Thus our Biomed 2 grant was launched with the aim of further improving the schemes themselves and promotion of participation of as many European IEM labs as possible.

Sub-project 1, QAP and Educational Programme

a) List of European IEM labs

A list of European IEM labs has been assembled to attempt to ascertain why some labs do not participate in ERNDIM QC schemes.
It is clear that the list is not complete in part because many University Labs do not feel that they belong to the routine diagnostic community with its accepted QC component.
Assumed reasons for lack of participation in both the directory and QC schemes are
1. Primarily research activity of the laboratory
2. Reluctance of labs to list themselves on a European level although not at the national level.
3. Some laboratories performing relevant measurements are outside the IEM context - e.g. more concerned with risk factors, e.g. homocysteine.
4. The range of activities of some labs does not fit in with content of schemes.
5. Inertia or lack of motivation.

Recommendations

1) Publication of the list of IEM labs on the web site and provision to ERNDIM scheme organisers who should write to labs to encourage participation in their schemes.
2) Governments should recognise and clarify the distinction between the different roles of research laboratories which perform diagnosis versus routine service labs.
3) National accreditation schemes should insist on participation in QC schemes which meet the criteria for IEM's (ie ERNDIM schemes which are the only ones with sufficiently large numbers).
   ERNDIM should write to National accreditation schemes informing them which QC schemes are available.
4) Additional schemes for QC in IEMs at the metabolite, protein and DNA level should be established.
5) Existing and future schemes should be more attuned to the needs of labs performing a small spectrum of tests and be more adaptable in offering a reduced spectrum of analytes.

b) Newborn Screening laboratories

Progress: A meeting between ERNDIM representatives and members of the so called EWS (European working Standards Group) was held recognising the problems of harmonising neonatal screening programmes and in setting up a European wide quality assessment programme. This Biomed 2 initiative has pointed the way forward and led to the establishment of the formal executive body, the European Screening Working Group with ERNDIM, International Neonatal Screening Society and other representatives.

Recommendation

There should be a European wide scheme for QA for newborn screening with clear distinction between screening and diagnostic laboratories.
It is evident that during the time of the Biomed 2 grant there have been significant developments or changes in the nature of screening possibilities with respect to sample matrix, range of diseases and methodology in some member countries.
It is therefore recommended that the criteria for whole population screening be critically re-evaluated in the light of original recommendations (WHO Technical Report Series #401, Publ Hlth Papers #34)) and in response to new technological developments.

c) Poor performers

Much information has been accumulated through the various QC schemes to allow the establishment of procedures in response to poor performance.
For the qualitative OA scheme the policy at the moment is only to deal with UK participants due to lack of systems to deal with European/worldwide participants. The procedure involves informing the laboratory, initiating measures to improve performance and if this does not result in improvement the UK Chemical Pathology Panel would be informed.

Recommendations

Formal specific action measures must be established by scheme organisers in response to poor performance. Ultimately sanctions should be instituted by instigation of steps involving the national accreditation board to which a laboratory is affiliated. Poor performance policies should be harmonised for all ERNDIM schemes.

Sub-Project 2: Development of proficiency testing in the Northern and Southern part of Europe

The establishment of proficiency schemes for Northern and Central Europe alongside that already existing for the Belgium/Netherlands/Germany has been completely successful.

Recommendations

Existing proficiency schemes need to be continued and if necessary new ones established to allow all appropriate labs to take part.
These should be harmonised through the newly established ERNDIM Scientific Advisory Board.
The nature of proficiency schemes is such that the number of participants needs to be kept small (20 – 25), to maintain the maximum exchange between and feedback to participants. This is in contrast to the larger numbers required for performance schemes.
The Proficiency Schemes need to be geographically compact and the possible need for additional centres is recognised.

Sub-Project 3: Documentation

A new directory of European IEM laboratories has been successfully assembled but questions regarding rare chemicals and standards and methods used could not be included. Also the assessment of the validity of laboratories by National Experts was not successfully achieved, since this task is virtually impossible for many National Experts due to several reasons including insufficient knowledge or political considerations.

Recommendations

The directory should be maintained on the SSIEM web site allowing for regular updating of existing centres and addition of new laboratories.
The participation of individual laboratories in QC schemes should be indicated.
It should be clearly stated as a qualification of the listed information that we cannot reveal any laboratories which may have a poor reputation, due to needs for local collaboration.
National accreditors/certifiers should be made aware of participation in existing QC schemes in assessing all laboratories.
Information included in the directory should be passed to accrediting authorities and they should be made aware of which tests are covered by our QC-schemes. A future aim is that only laboratories accredited by European norms should be included in the directory.

Sub-Project 4: Introduction of a reference standard for calibration of amino acids

Analysis of results from the different QC schemes showed that problems of imprecision were mainly related to pre-analytical variations and not only to the standard reference material employed.
Therefore in addressing the actual problems we have developed a good laboratory practice document for amino acid analysis to be recommended to all participants.
P. Kamoun has prepared one of the test samples for the amino acid scheme for 2000 to be provided as a reference material with consensus values for internal quality control.

Recommendations

1. A standard operating procedure for amino acids supported by the ERNDIM board should be distributed to all ERNDIM participants and also mounted on the web site.
2. Standard operating procedures should also be produced for other methods relevant to the ERNDIM QC-schemes.
3. Calibration material is lacking and can lead to imprecision in some instruments. We recommend that DG3 of the EU should take on the remit of developing such standards, especially to include rare organic acids which are not commercially available.

Sub-Project 5: Establishment of age- and diet-related reference values for the main IDM metabolites in body fluids

The aims of this part of the project were not fulfilled.
A major practical problem is that for ethical reason it is extremely difficult to obtain sufficient numbers of blood samples from infants and children for each age class to establish reliable and useful reference values according to the IFCC recommendations. Work is in progress to obtain data from existing nutritional investigations for 1, 2 and 4 months of age to establish reference values in that age group where major changes in amino acid concentrations occur. The choice of the age stratification is a further problem, because opportunistic approaches by establishing the reference intervals for those age classes where blood is "easily" available (e.g. cord blood) prevail. The need to establish reference values for 2- 5 years of age still exists but represents a major problem simply due to difficulties in obtaining blood.
Pooling data from different laboratories, as done in the past in Germany for usual clinical chemistry parameters, is plagued by additional discrepancies introduced by inter-laboratory variation.

Recommendations

There needs to be increased awareness of possible inter-laboratory variation in metabolite values in interpreting data in collaborative studies. When inter-laboratory variation is improved programmes should be established to obtain consensus control values and agreed critical levels for decisions for diagnostic purposes and for treatment monitoring. Efforts to establish reference data: 1) in random urine samples between 1 month and 2.5 years (until the creatinine excretion stabilises) should be encouraged; 2) For blood samples as outlined above.

Sub-Project 6: Newsletter

The first two Newsletters have been circulated according to schedule and No 3 is in the final editing stage and almost ready to be distributed (Title: The control of analytical accuracy and day to day precision helps for the follow-up of patients and is essential when using biochemical data from the literature). No 4 will be based on the conclusions and recommendations resulting from Biomed 2.

Recommendations

1. GLP recommendations, standards, guidelines on which to use and recommended normal ranges should be compiled and distributed as part of the continuing educational aspect of the QC schemes.
2. Future educational activities related to QC schemes should continue to include Newsletters.

These educational documents should be produced in hard copy as well as electronic forms and promoted to encourage interaction between scheme organisers and participants for discussion of related issues.

Sub-Project 7: Meetings

All aims have been achieved with successful holding of National QC meetings, workshops at the SSIEM as well as regular meetings of the ERNDIM Board and of the Executive Committee.

Recommendations

Meetings to allow dialogue and interaction between the ERNDIM Board, the scheme organisers and participants should be continued. Workshops and presentation of scientific results should be furthered and in particular proficiency scheme discussions should be linked to other large international or regional/national meetings.
The various recommendations in this report could be suitable for evaluation and discussion in future ERNDIM workshops.