DEFINING WHAT IS A SATISFACTORY BODY OF EVIDENCE FOR AUTOLOGOUS CELL BASED HUMAN INTERVENTIONS

NBOT ANNUAL WORKSHOP

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The Practice of Medicine

• This is an art guided by science

• Patient relationship is important

• The laying on of hands plays a significant role in treatment

• Much of the science is empirical

• Treatment based on evidence is important, but is only one factor in treatment

• If evidence from controlled trials was a prerequisite for ALL treatments, the practice of traditional medicine as we know it would cease.
Complementary Medicines

• This is a growing industry, despite there being none or very little evidence based on double blinded control studies that the products work

• Blackmores Limited
The modern era of transplantation began in the 1960s with the introduction of anti-rejection drugs.

Successful heart transplants began in 1967 with Christiaan Barnard operating on Louis Washkansky in a highly experimental situation.

Control trials were not carried out to advance the field, progress being based on clinical experience and animal studies.

Phase 1b/2a clinical trials are uncontrolled, aiming to show safety and some efficacy.
**Cell Therapies**

- Xenotransplants require regulatory oversight.

- Allotransplants require HREC approval but not TGA oversight.

- Autotransplants are generally excluded from regulatory oversight – TGA Excluded Goods Order
  - With some animal evidence, and some patients appearing to benefit from autologous cell therapies, this has led to the growth of an industry
  - It is driven by patient need
  - It costs
  - It needs regulating to avoid unscrupulous operators fleecing gullible members of the public
Voluntary Code of Conduct

A group of operators involved in autologous cell interventions came together and paid for the creation of a Code of Practice in Feb 2015.

AUSTRALIAN CELL THERAPY SOCIETY

THE USE OF AUTOLOGOUS CELL-BASED INTERVENTIONS BY MEDICAL PRACTITIONER’S UNDER THE THERAPEUTIC (EXCLUDED GOODS) ORDER NO.1 OF 2011.

CODE OF PRACTICE

FEBRUARY, 2015

3.1 The evaluation and practice of ACBIs shall adhere to principles of evidence-based medicine.

3.2 Members shall document the evaluation of ACBIs prior to treating patients in medical practice.

Evaluation of an ACBI shall be guided by NHMRC evidence-based clinical practice guidelines and include thorough analysis of the results, strengths and weaknesses of the best available evidence. This shall form the basis for the evaluation of benefits versus risks.

Evaluation shall also include consideration of potential regulatory, ethical, financial and operational requirements.
Code of Practice

3.3 An ACBI should meet the following minimum criteria prior to routine use outside the context of clinical trials, particularly when large numbers of patients are to be treated and charged for such services:

Safety – is supported by 2-3 independent human safety studies, of an adequate number of patients.

Efficacy – is supported by a ‘satisfactory body of evidence’ or better, demonstrating the effectiveness of the intervention in the disease area. This is defined in Table 1 NHMRC’s “Additional levels of evidence and grades for recommendations for developers of guidelines”

Quality – is supported by validated protocols and release specifications and compliance with recommended Safety and Quality Standards.

In all such cases patients must be appropriately informed about the ACBI.
# NHMRC Body of Evidence Matrix

## Table 1  Body of evidence matrix

<table>
<thead>
<tr>
<th>Component</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence base¹</td>
<td>one or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td>
<td>one or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias</td>
<td>one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias</td>
<td>level IV studies, or level I to III studies/SRs with a high risk of bias</td>
</tr>
<tr>
<td>Consistency²</td>
<td>all studies consistent</td>
<td>most studies consistent and inconsistency may be explained</td>
<td>some inconsistency reflecting genuine uncertainty around clinical question</td>
<td>evidence is inconsistent</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>very large</td>
<td>substantial</td>
<td>moderate</td>
<td>slight or restricted</td>
</tr>
<tr>
<td>Generalisability</td>
<td>population/s studied in body of evidence are the same as the target population for the guideline</td>
<td>population/s studied in the body of evidence are similar to the target population for the guideline</td>
<td>population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population³</td>
<td>population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population</td>
</tr>
<tr>
<td>Applicability</td>
<td>directly applicable to Australian healthcare context</td>
<td>applicable to Australian healthcare context with few caveats</td>
<td>probably applicable to Australian healthcare context with some caveats</td>
<td>not applicable to Australian healthcare context</td>
</tr>
</tbody>
</table>

1. Evidence base
2. Consistency
3. Generalisability

Source: [NHMRC Body of Evidence Matrix](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)
### NHMRC Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention</th>
<th>Diagnostic accuracy</th>
<th>Prognosis</th>
<th>Aetiology</th>
<th>Screening intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
</tr>
<tr>
<td>II</td>
<td>A randomised controlled trial</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation</td>
<td>A prospective cohort study</td>
<td>A prospective cohort study</td>
<td>A randomised controlled trial</td>
</tr>
<tr>
<td>III-1</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation</td>
<td>All or none</td>
<td>All or none</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
</tr>
<tr>
<td>III-2</td>
<td>A comparative study with concurrent controls:</td>
<td>A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence</td>
<td>Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial</td>
<td>A retrospective cohort study</td>
<td>A comparative study with concurrent controls:</td>
</tr>
</tbody>
</table>
|       | • Non-randomised, experimental trial  
|       | • Cohort study                                  |                                                          |                                               |                                               | • Non-randomised, experimental trial  
|       | • Case-control study                            |                                                          |                                               |                                               | • Cohort study                           |
|       | • Interrupted time series with a control group |                                                          |                                               |                                               | • Case-control study                      |
| III-3 | A comparative study without concurrent controls: | Diagnostic case-control study  
|       | • Historical control study                      |                                                          | A retrospective cohort study                   | A case-control study                        | A comparative study without concurrent controls:  |
|       | • Two or more single arm study                  |                                                          |                                               |                                               | • Historical control study                |
|       | • Interrupted time series without a control group|                                                          |                                               |                                               | • Two or more single arm study            |
| IV    | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard)  
|       |                                                 |                                                          | Case series, or cohort study of persons at different stages of disease | A cross-sectional study or case series       | Case series                              |

[Source](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)
Snap Shot of Australian Stem Cell Companies

Companies included were those:
• conducting a clinical trial, with approval of a Human Research Ethics Committee, and was in a Clinical Trial Registry.
• licenced by the TGA to produce a product to be used clinically.
• selling products used in research, and not for clinical interventions.

Not included were those conducting clinical interventions with no published evidence for these.

Not included but possibly could, in the 2nd Edition, were those conducting:
• clinical interventions with evidence previously published in peer reviewed journals.
• veterinary interventions.
CRITICAL LIMB ISCHAEMIA

- Age 76
- Type 1 diabetes 55 years
- Progressive peripheral vascular disease
- Peripheral neuropathy
- Bladder cancer – ureterostomy
- Depression
- Treatment: revascularization by angioplasty & vascular bypass; wound debridement; removal of dead/dying tissue; Lipidil (FIELD study)
- No proven cell therapies; control trials underway overseas but none in Australia; animal studies suggest a benefit
PATHWAY FORWARD

• This is a very fluid situation
• There are competing views
  (a) no treatment unless evidence based: Scientist
  (b) stem cell tourism – leave no stone unturned: Patient & family
  (c) medicine is an art, not just a science: Clinician
• Important to keep all players around the table communicating with one another