Improving patient outcome after stem cell transplantation: the importance of clinical trial

C Craddock
The clinical application of Advances in Fundamental Science has Transformed Patient Outcome in Chronic Myeloid Leukaemia
Rapid assessment of novel therapies: a global challenge

- The last decade has seen a revolution in diagnostics and therapeutics which is transforming patient outcome.
- As a consequence rapid and accurate assessment of novel therapies is now an urgent medical priority.
- The infrastructure and capacity for clinical trial delivery have not kept pace and remain very similar to a decade ago.
- Consequently assessment of novel therapies is slow and this global deficit represents a major challenge to pharma.
- Thus our obligations to patients are not being met and the UK is missing an opportunity to become the destination of choice for drug development.

- Stem cell transplantation is an increasingly important curative treatment modality for children and adults.
- Despite significant advances in donor selection and supportive care, many patients die of recurrent disease or toxicity.
- Disease relapse, infection, GVHD and late effects remain major causes of post-transplant morbidity and mortality.
- There remain major unanswered questions concerning optimal transplant protocols and there is also great variation in practice.
- <5% of patients enter prospective transplant trials.
Causes of Death after HLA-identical Sibling Transplants done in 2010-2011

- Primary Disease: 49%
- GVHD: 17%
- Infection: 15%
- Organ Failure: 12%
- Second Malignancy: 5%
- Other: 1%
Causes of Death after Unrelated Donor Transplants done in 2010-2011

- Primary Disease: 38%
- GVHD: 17%
- Infection: 17%
- Organ Failure: 17%
- Second Malignancy: 7%
- Other: 1%

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
What can be done to accelerate improvement in patient outcomes (i)?

- Improve data collection and support local quality management systems
- Encourage adoption of standardised transplant regimens with attention to critical issues such as intensity and duration of immunosuppression, frequency and nature of chimerism monitoring and DLI schedules
- Resource a forum by which consensus around standard regimens and regular of assessments of their clinical activity is monitored
What can be done to accelerate improvement in patient outcomes (ii)?

- Deliver practice changing randomised trials which address main causes of transplant failure
- Embed genomic stratification and biomarkers into clinical studies
- Strengthen and empower national and international trials networks
- Build translational partnerships between the biopharmaceutical industry and transplant networks
Increased availability of allogeneic transplants: the status of reduced intensity conditioning (RIC) regimens in 2016

Accumulating data confirm RIC regimen deliver:
- a marked reduction in transplant related mortality achieved in both sibling and unrelated donors transplants
- a potentially curative GVL effect can now be delivered in patients up to the age of 70
- high rates of GVHD remain a major challenge

The critical questions yet to be answered are:
- what is the optimal RIC regimen in AML?
- is there a differential impact of RIC regimens on relapse and GVHD
- what is the optimal GVHD prophylaxis regimen?
Survival from RIC transplant. Sibling vs MUD

Russell et al
Survival from CR in Patients with AML Age 40-6 who have adverse risk cytogenetics

Russell et al 2012
Figaro Trial Overview

170 Patients randomised 1:1 and consented for trial

Patients stratified by the following:
- Underlying disease (AML; MDS)
- Cytogenetic risk group (adverse risk; intermediate or good risk)
- Disease status at transplant (CR1 or CR2; primary refractory disease)
- Age (>60; ≤60 years)
- Donor type (sibling; unrelated)
- Intended control arm (FMA; FBA; FB-ATG)

Control Arm
- Fludarabine/melphalan/alemtuzumab (FMA) transplant conditioning
- OR Fludarabine/busulphan/alemtuzumab (FBA) transplant conditioning
- OR Fludarabine/busulphan/ATG (FB-ATG)

Experimental arm
- Fludarabine/cytarabine/amsacrine/busulphan/ATG (FLAMSA-BU) transplant conditioning

Day 0
- Peripheral blood/bone marrow stem cell transplantation

Day 100, 12 months
- Assessment of transplant related mortality (TRM)

Primary endpoint assessment (continually until 24 months)
- Overall survival (OS)

Secondary endpoints assessment (continually until 24 months)
- Disease free survival (DFS), disease relapse
Current Status of Trial – Cumulative Recruitment

Target number of patients Jun 2016 - 200

Cumulative Target
Cumulative Recruitment

Total recruited

Sample Return Rate

• Samples expected - 142
• Samples received – 377
  – 92% return rate

- MFC-MRD LAIP / LMPP-LSC – prospectively assessed
- (integrated with information from MRD monitoring of NCRI AML trials)
  Snapshot of data up to Trial No 131 - 371 samples assessed (Oct 13 – Jan 15)
- Pre-Transplant  107 samples (~16% inadequate, ~ 28% no previous LAIP)
- Post-Transplant  264 samples (~8% inadequate)
  (D42=99 3months=69 6months=59 9months=25  12months=12)
How can we increase the number of patients entering prospective studies in the UK?

- The BSBMT CTC has made a major contribution to clinical transplant research through retrospective studies.
- Development of prospective trials has been challenging.
- <10% UK transplant patients enter trials addressing how to improve outcome of transplant - only open studies are funded by LLR and CRUK.
- Patients are failing to benefit in a timely fashion from therapeutic advances.
Requirements for an Internationally Competitive Transplant Trials Programme: opportunities for the UK

✓ High quality clinical teams, committed to clinical innovation

✓ Strong national registry: BSBMT CTC

✓ Large catchment region

✓ Strong, translationally focused basic science programme

✗ Appropriately resourced trials network with sufficient population to deliver trials to time and target

✗ Regulatory hub ensuring prompt work-up of studies

✗ Research nurse support in busy regional transplant centres to ensure rapid recruitment
“The Life Sciences now represents a multi-billion pound industry which the UK is uniquely placed to lead”
The Future of Unrelated Donor Stem Cell Transplantation in the UK

Part 1
Findings and Recommendations

A Report from the UK Stem Cell Strategic Forum
July 2019
www.nhsbt.nhs.uk

Part 2
Annexes

A Report from the UK Stem Cell Strategic Forum
July 2019
www.nhsbt.nhs.uk
Given the significant mortality of unrelated donor transplantation it is highly desirable that transplants are performed according to disease specific registration studies and where possible appropriately badged clinical trials

Commissioning authorities should encourage the development of appropriate studies for patients undergoing unrelated donor transplantation
Substantial Government funding over the last two decades has resulted in the development of a world-class science base in stem cell biology in the U.K. A clinical trials network of centres performing unrelated donor stem cell transplants should be established. This will create one of the world’s largest stem cell transplant trials networks.

Collaborative links should be established between donor registries, cord blood banks and the biopharmaceutical industries. This initiative, coupled with the establishment of a clinical trials network has the capacity to attract inward investment in the U.K which will create jobs in the knowledge rich biotechnology sector.
BMT CTN Organizational Structure

- Protocol Review Committee
- Data and Safety Monitoring Board
- NCI Coop Group Chairs (ex officio)
- 20 Clinical Cores; High-performing Affiliate Centers
- Administrative Committees
- Technical Committees
- Protocol Teams
- Data and Coordinating Center
- Affiliate Clinical Centers
>115 centers have enrolled >6,000 patients since 2003

- **Core Centers**
- **PBMTC Centers**
- **Affiliate Centers**
Early and ongoing collaboration with cooperative groups to synergize and avoid duplication (intensified since 2005)

N of pts = 450 1,050 1,625 2,150 2,625 3,050 3,450 4,300 6,000

- Developed infrastructure

Opened this grant cycle (8/11):
0903: Allo for HIV-malignancy
1101: Haplo vs Double Cord
1202: Biomarker collection
1204: RIC for HLH

- 33 Protocols Opened (9 currently open)
- 27 BMT CTN-led
- 6 Cooperative Group-led

1205: Patient-friendly Consent
1304: Early vs Late HCT for MM
1102: HCT vs Chemo for MDS

TRIALS OPEN FOR ENROLLMENT 2001-2013

= Enrollment complete
= Enrollment on-going
= Cumulative actual [projected] accrual
= Coop group collaboration (see color key above)
### BMT CTN TRIALS - SUMMARY

<table>
<thead>
<tr>
<th>Category</th>
<th>All Trials</th>
<th>Phase II</th>
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<tr>
<td>Donor/Graft Source</td>
<td>13</td>
<td>8</td>
<td>6</td>
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<tr>
<td>GVHD</td>
<td>5</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Infection</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Disease Control</td>
<td>14</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Regimen Toxicity</td>
<td>5</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>QOL</td>
<td>8</td>
<td>3</td>
<td>4</td>
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<td><strong>TOTAL</strong></td>
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<td><strong>15</strong></td>
<td><strong>17</strong></td>
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</tbody>
</table>

* Includes Biomarker protocol for specimen collection
UK Trials Acceleration Programme (TAP)

Aims of TAP:-

- Create the capacity and confidence to deliver early phase trials on a new scale
- Provide increased access to innovative treatments
- Strengthen translational research

Achievement's to date:-

- 14 trials opened
- Secured approximately £200 million worth of free drug
- Rapid recruitment of over 600 patients to early phase trials over a 3 year period
### Summary of time to trial set-up

<table>
<thead>
<tr>
<th>Trial</th>
<th>Award date</th>
<th>Date trial opened to recruitment</th>
<th>Days to opening</th>
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<tbody>
<tr>
<td>MAJIC</td>
<td>01-Oct-2011</td>
<td>09-Aug-2012</td>
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<tr>
<td>RAvVA</td>
<td>01-Oct-2011</td>
<td>28-Sep-2012</td>
<td>363</td>
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<td>Brevity</td>
<td>25-Nov-2011</td>
<td>10-Feb-2014</td>
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<tr>
<td>CyCLLe</td>
<td>29-Mar-2012</td>
<td>29-Apr-2013</td>
<td>396</td>
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<tr>
<td>RomAZA</td>
<td>22-Nov-2012</td>
<td>30-Sep-2013</td>
<td>312</td>
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<tr>
<td>VIOLA</td>
<td>08-Apr-2013</td>
<td>05-Feb-2014</td>
<td>303</td>
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<tr>
<td>IciCLLe</td>
<td>29-Mar-2012</td>
<td>12-Jun-2014</td>
<td>805*</td>
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<tr>
<td>ELASTIC</td>
<td>22-Nov-2012</td>
<td>15-Oct-2014</td>
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<tr>
<td>MATCHPOINT</td>
<td>22-Nov-2012</td>
<td>02-Dec-2014</td>
<td>740*</td>
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<tr>
<td>TIER</td>
<td>27-Nov-2013</td>
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<td>CALIBRE</td>
<td>29-Mar-2012</td>
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<tr>
<td>RomiCAR</td>
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<td>13-Jul-2015</td>
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*significant unexpected delays incurred by Pharmaceutical Industry, Including but not limited to contractual delays, takeovers, safety issues arising from drug in question
# Summary of TAP recruitment

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<tr>
<th>Trial</th>
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<th>Recruitment to date</th>
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<td>MAJIC</td>
<td>306 (290 previously)</td>
<td>262</td>
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<tr>
<td>RAvVA</td>
<td>260 (160 previously)</td>
<td>260</td>
</tr>
<tr>
<td>Brevity</td>
<td>30 (+ extension)</td>
<td>38</td>
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<tr>
<td>CyCLLe</td>
<td>10</td>
<td>5</td>
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<tr>
<td>RomAZA</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td>VIOLA</td>
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<td>14</td>
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<tr>
<td>IciCLLe</td>
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<td>40</td>
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<tr>
<td>ELASTIC</td>
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<tr>
<td>CALIBRE</td>
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<tr>
<td>RomiCAR</td>
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<tr>
<td>TORCH</td>
<td>36</td>
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655 PATIENTS RECRUITED IN 3 YEARS (COMPARSES with 5 (2000-2005)
RAvVA has fully recruited to target of 260 patients in less than 3 years

Largest trial of epigenetic therapy in AML in the world
UPTAKE: an opportunity to create a globally significant transplant trials network

- Stem cell transplantation represents the only curative therapy for large numbers of children and adults with haematological malignancies
- Advances in transplant therapy have provided much of the intellectual and clinical grounding for recent advances in immunotherapy and regenerative medicine
- Despite the almost universal availability of stem cell donors many patients die of transplant toxicity or disease
- <5% of patients enter prospective transplant trials
Proposed structure of UPTAKE

Central Hub
- Responsible for trial design, setup, management and publication
- 10 transplant centres are able to recruit to BSBMT transplant studies

Specialist Transplant Centres
- Able to recruit to Cell Therapy Catapult trials
Gantt chart of predicted development of the UPTAKE trial portfolio

<table>
<thead>
<tr>
<th>Trial</th>
<th>Event</th>
<th>Year</th>
<th>Quarter</th>
<th>Event</th>
<th>Year</th>
<th>Quarter</th>
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<td>Follow-up</td>
<td>2016</td>
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<td>3</td>
<td>Recruitment</td>
<td>2016</td>
<td>Q3</td>
<td>Publication</td>
<td>2016</td>
<td>Q3</td>
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<td>4</td>
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<td>2016</td>
<td>Q4</td>
<td>Follow-up</td>
<td>2016</td>
<td>Q4</td>
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<td>5</td>
<td>Recruitment</td>
<td>2017</td>
<td>Q1</td>
<td>Follow-up</td>
<td>2017</td>
<td>Q1</td>
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<tr>
<td>6</td>
<td>Recruitment</td>
<td>2017</td>
<td>Q2</td>
<td>Follow-up</td>
<td>2017</td>
<td>Q2</td>
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<tr>
<td>7</td>
<td>Recruitment</td>
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<td>Follow-up</td>
<td>2017</td>
<td>Q3</td>
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<td>8</td>
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<td>Follow-up</td>
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<td>Follow-up</td>
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<td>Follow-up</td>
<td>2018</td>
<td>Q4</td>
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<td>Follow-up</td>
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<td>Q4</td>
<td>Follow-up</td>
<td>2021</td>
<td>Q4</td>
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**Key**
- Set-up (9 months)
- Recruitment (2 years)
- Follow-up (2 years)
- Publication (6 months)
## Deliverables

- **Key deliverables of 4 year programme by Dec 2020**

<table>
<thead>
<tr>
<th></th>
<th>No. of trials set-up/opened</th>
<th>No. of trials fully recruited</th>
<th>Number of trials ready for publication</th>
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<tbody>
<tr>
<td>BSBMT trials</td>
<td>12</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Cell Therapy Catapult trials</td>
<td>12</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>24</strong></td>
<td><strong>15</strong></td>
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</table>

- **Key deliverables of 4 year programme by Dec 2024**

<table>
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<tr>
<th></th>
<th>No. of trials set-up/opened</th>
<th>No. of trials fully recruited</th>
<th>Number of trials submitted for publication</th>
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<tr>
<td>BSBMT trials</td>
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<td>12</td>
<td>12</td>
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<tr>
<td>Cell Therapy Catapult trials</td>
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<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>24</strong></td>
<td><strong>24</strong></td>
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</table>
Summary

- Consensus National transplant trial model approved by all partners

- UPTAKE will transform the U.K.’s ability to deliver transplant and immunotherapy studies by creating a fit for purpose world class translational model

- UPTAKE will drive innovation in transplant and immunotherapy and improve patient outcomes-permitting access to £100s million novel therapies

- UPTAKE will create opportunities for delivery of practice changing biomarker and scientific studies

- Project team appointed with the aim of opening UPTAKE Q4 2016