The Big Four Bulletin
3 January 2018 No. 567

Contents

BMJ

The BMJ has produced no new content this week.

JAMA: The Journal of the American Medical Association (2 January 2018)

- Effect of Mechanically Expanded vs Self-Expanding Transcatheter Aortic Valve Replacement on Mortality and Major Adverse Clinical Events in High-Risk Patients With Aortic Stenosis: The REPRISE III Randomized Clinical Trial
- Effect of Hydrolyzed Infant Formula vs Conventional Formula on Risk of Type 1 Diabetes: The TRIGR Randomized Clinical Trial
- Association of Race and Ethnicity With Live Donor Kidney Transplantation in the United States From 1995 to 2014

The Lancet

The Lancet has produced no new content this week.

The New England Journal of Medicine (28 December 2017)

- AAV5–Factor VIII Gene Transfer in Severe Hemophilia A
- Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma
- Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas
- Safety of Magnetic Resonance Imaging in Patients with Cardiac Devices

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BMJ

The BMJ has produced no new content this week.

Back to Contents

JAMA: Journal of the American Medical Association (2 January 2018, Vol. 319, No. 1)

Effect of Mechanically Expanded vs Self-Expanding Transcatheter Aortic Valve Replacement on Mortality and Major Adverse Clinical Events in High-Risk Patients With Aortic Stenosis: The REPRISE III Randomized Clinical Trial

Ted E. Feldman, Michael J. Reardon, Vivek Rajagopal, et al

JAMA. 2018; 319 (1): 27-37.
https://jamanetwork.com/journals/jama/article-abstract/2667721?redirect=true

Abstract

Importance Transcatheter aortic valve replacement (TAVR) is established for selected patients with severe aortic stenosis. However, limitations such as suboptimal deployment, conduction disturbances, and paravalvular leak occur.

Objective To evaluate if a mechanically expanded valve (MEV) is noninferior to an approved self-expanding valve (SEV) in high-risk patients with aortic stenosis undergoing TAVR.

Design, Setting, and Participants The REPRISE III trial was conducted in 912 patients with high or extreme risk and severe, symptomatic aortic stenosis at 55 centers in North America, Europe, and Australia between September 22, 2014, and December 24, 2015, with final follow-up on March 8, 2017.

Interventions Participants were randomized in a 2:1 ratio to receive either an MEV (n = 607) or an SEV (n = 305).

Main Outcomes and Measures The primary safety end point was the 30-day composite of all-cause mortality, stroke, life-threatening or major bleeding, stage 2/3 acute kidney injury, and major vascular complications tested for noninferiority (margin, 10.5%). The primary effectiveness end point was the 1-year composite of all-cause mortality, disabling stroke, and moderate or greater paravalvular leak tested for noninferiority (margin, 9.5%). If noninferiority criteria were met, the secondary end point of 1-year moderate or greater paravalvular leak was tested for superiority in the full analysis data set.

Results Among 912 randomized patients (mean age, 82.8 [SD, 7.3] years; 463 [51%] women; predicted risk of mortality, 6.8%), 874 (96%) were evaluable at 1 year. The primary safety composite end point at 30 days occurred in 20.3% of MEV patients and 17.2% of SEV patients (difference, 3.1%; Farrington-Manning 97.5% CI, −∞ to 8.3%; $P = .003$ for noninferiority). At 1 year, the primary effectiveness composite end point occurred in 15.4% with the MEV and 25.5% with the SEV (difference, −10.1%; Farrington-Manning 97.5% CI, −∞ to −4.4%; $P<.001$ for noninferiority). The 1-year rates of moderate or severe paravalvular leak were 0.9% for the MEV and 6.8% for the SEV (difference, −6.1%; 95% CI, −9.6% to −2.6%; $P < .001$). The superiority analysis for primary effectiveness was statistically significant (difference, −10.2%; 95% CI, −16.3% to −4.0%; $P < .001$). The MEV had higher rates of new pacemaker implants (35.5% vs 19.6%; $P < .001$) and valve thrombosis (1.5% vs 0%) but lower rates of repeat procedures (0.2% vs 2.0%), valve-in-valve deployments (0% vs 3.7%), and valve malpositioning (0% vs 2.7%).

Conclusions and Relevance Among high-risk patients with aortic stenosis, use of the MEV compared with the SEV did not result in inferior outcomes for the primary safety end point or the primary effectiveness end point. These findings suggest that the MEV may be a useful addition for TAVR in high-risk patients.

Effect of Hydrolyzed Infant Formula vs Conventional Formula on Risk of Type 1 Diabetes: The TRIGR Randomized Clinical Trial

Writing Group for the TRIGR Study Group

JAMA. 2018; 319 (1): 38-48.
https://jamanetwork.com/journals/jama/article-abstract/2667723?redirect=true

Abstract

Importance Early exposure to complex dietary proteins may increase the risk of type 1 diabetes in children with genetic disease susceptibility. There are no intact proteins in extensively hydrolyzed formulas.

Objective To test the hypothesis that weaning to an extensively hydrolyzed formula decreases the cumulative incidence of type 1 diabetes in young children.

Design, Setting, and Participants An international double-blind randomized clinical trial of 2159 infants with human leukocyte antigen–conferred disease susceptibility and a first-degree relative with type 1 diabetes recruited from May 2002 to January 2007 in 78 study centers in 15 countries; 1081 were randomized to be weaned to the extensively hydrolyzed casein formula and 1078 to a conventional formula. The follow-up of the participants ended on February 28, 2017.

Interventions The participants received either a casein hydrolysate or a conventional adapted cow's milk formula supplemented with 20% of the casein hydrolysate. The minimum duration of study formula exposure was 60 days by 6 to 8 months of age.

Main Outcomes and Measures Primary outcome was type 1 diabetes diagnosed according to World Health Organization criteria. Secondary outcomes included age at diabetes diagnosis and safety (adverse events).

Results Among 2159 newborn infants (1021 female [47.3%]) who were randomized, 1744 (80.8%) completed the trial. The participants were observed for a median of 11.5 years (quartile [Q] 1-Q3, 10.2-12.8). The absolute risk of type 1 diabetes was 8.4% among those randomized to the casein hydrolysate (n = 91) vs 7.6% among those randomized to the conventional formula (n = 82) (difference, 0.8% [95% CI, −1.6% to 3.2%]). The hazard ratio for type 1 diabetes adjusted for human leukocyte antigen risk group, duration of breastfeeding, duration of study formula consumption, sex, and region while treating study center as a random effect was 1.1 (95% CI, 0.8 to 1.5; *P* = .46). The median age at diagnosis of type 1 diabetes was similar in the 2 groups (6.0 years [Q1-Q3, 3.1-8.9] vs 5.8 years [Q1-Q3, 2.6-9.1]; difference, 0.2 years [95% CI, −0.9 to 1.2]). Upper respiratory infections were the most common adverse event reported (frequency, 0.48 events/year in the hydrolysate group and 0.50 events/year in the control group).

Conclusions and Relevance Among infants at risk for type 1 diabetes, weaning to a hydrolyzed formula compared with a conventional formula did not reduce the cumulative incidence of type 1 diabetes after median follow-up for 11.5 years. These findings do not support a need to revise the dietary recommendations for infants at risk for type 1 diabetes.

Association of Race and Ethnicity With Live Donor Kidney Transplantation in the United States From 1995 to 2014

Tanjala S. Purnell, Xun Luo, Lisa A. Cooper, et al

JAMA. 2018; 319 (1): 49-61.
https://jamanetwork.com/journals/jama/article-abstract/2667722?redirect=true

Abstract

Importance Over the past 2 decades, there has been increased attention and effort to reduce disparities in live donor kidney transplantation (LDKT) for black, Hispanic, and Asian patients with end-stage kidney disease. The goal of this study was to investigate whether these efforts have been successful.

Objective To estimate changes over time in racial/ethnic disparities in LDKT in the United States, accounting for differences in death and deceased donor kidney transplantation.

Design, Setting, and Participants A secondary analysis of a prospectively maintained cohort study conducted in the United States of 453 162 adult first-time kidney transplantation candidates included in the Scientific Registry of Transplant Recipients between January 1, 1995, and December 31, 2014, with follow-up through December 31, 2016.

Exposures Race/ethnicity.

Main Outcomes and Measures The primary study outcome was time to LDKT. Multivariable Cox proportional hazards and competing risk models were constructed to assess changes in racial/ethnic disparities in LDKT among adults on the deceased donor kidney transplantation waiting list and interaction terms were used to test the statistical significance of temporal changes in racial/ethnic differences in receipt of LDKT. The adjusted subhazard ratios are estimates derived from the multivariable competing risk models. Data were categorized into 5-year increments (1995-1999, 2000-2004, 2005-2009, 2010-2014) to allow for an adequate sample size in each analytical cell.

Results Among 453 162 adult kidney transplantation candidates (mean [SD] age, 50.9 [13.1] years; 39% were women; 48% were white; 30%, black; 16%, Hispanic; and 6%, Asian), 59 516 (13.1%) received LDKT. Overall, there were 39 509 LDKTs among white patients, 8926 among black patients, 8357 among Hispanic patients, and 2724 among Asian patients. In 1995, the cumulative incidence of LDKT at 2 years after appearing on the waiting list was 7.0% among white patients, 3.4% among black patients, 6.8% among Hispanic patients, and 5.1% among Asian patients. In 2014, the cumulative incidence of LDKT was 11.4% among white patients, 2.9% among black patients, 5.9% among Hispanic patients, and 5.6% among Asian patients. From 1995-1999 to 2010-2014, racial/ethnic disparities in the receipt of LDKT increased ($P < .001$ for all statistical interaction terms in adjusted models comparing white patients vs black, Hispanic, and Asian patients). In 1995-1999, compared with receipt of LDKT among white patients, the adjusted subhazard ratio was 0.45 (95% CI, 0.42-0.48) among black patients, 0.83 (95% CI, 0.77-0.88) among Hispanic patients, and 0.56 (95% CI, 0.50-0.63) among Asian patients. In 2010-2014, compared with receipt of LDKT among white patients, the adjusted subhazard ratio was 0.27 (95% CI, 0.26-0.28) among black patients, 0.52 (95% CI, 0.50-0.54) among Hispanic patients, and 0.42 (95% CI, 0.39-0.45) among Asian patients.

Conclusions and Relevance Among adult first-time kidney transplantation candidates in the United States who were added to the deceased donor kidney transplantation waiting list between 1995 and 2014, disparities in the receipt of live donor kidney transplantation increased from 1995-1999 to 2010-2014. These findings suggest that national strategies for addressing disparities in receipt of live donor kidney transplantation should be revisited.

Back to Contents

The Lancet

The Lancet has produced no new content this week.

Back to Contents

The New England Journal of Medicine (28 December 2017, Vol. 377, No. 26)

AAV5–Factor VIII Gene Transfer in Severe Hemophilia A

Savita Rangarajan, Liron Walsh, Will Lester, et al.

N Engl J Med 2017; 377: 2519-2530 December 28, 2017
http://www.nejm.org/doi/full/10.1056/NEJMoa1708483

Summary

Background

Patients with hemophilia A rely on exogenous factor VIII to prevent bleeding in joints, soft tissue, and the central nervous system. Although successful gene transfer has been reported in patients with hemophilia B, the large size of the factor VIII coding region has precluded improved outcomes with gene therapy in patients with hemophilia A.

Methods

We infused a single intravenous dose of a codon-optimized adeno-associated virus serotype 5 (AAV5) vector encoding a B-domain–deleted human factor VIII (AAV5-hFVIII-SQ) in nine men with severe hemophilia A. Participants were enrolled sequentially into one of three dose cohorts (low dose [one participant], intermediate dose [one participant], and high dose [seven participants]) and were followed through 52 weeks.

Results

Factor VIII activity levels remained at 3 IU or less per deciliter in the recipients of the low or intermediate dose. In the high-dose cohort, the factor VIII activity level was more than 5 IU per deciliter between weeks 2 and 9 after gene transfer in all seven participants, and the level in six participants increased to a normal value (>50 IU per deciliter) that was maintained at 1 year after receipt of the dose. In the high-dose cohort, the median annualized bleeding rate among participants who had previously received prophylactic therapy decreased from 16 events before the study to 1 event after gene transfer, and factor VIII use for participant-reported bleeding ceased in all the participants in this cohort by week 22. The primary adverse event was an elevation in the serum alanine aminotransferase level to 1.5 times the upper limit of the normal range or less. Progression of preexisting chronic arthropathy in one participant was the only serious adverse event. No neutralizing antibodies to factor VIII were detected.

Conclusions

The infusion of AAV5-hFVIII-SQ was associated with the sustained normalization of factor VIII activity level over a period of 1 year in six of seven participants who received a high dose, with stabilization of hemostasis and a profound reduction in factor VIII use in all seven participants. In this small study, no safety events were noted, but no safety conclusions can be drawn.

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

Sattva S. Neelapu, Frederick L. Locke, Nancy L. Bartlett, et al.

N Engl J Med 2017; 377: 2531-2544 December 28, 2017
http://www.nejm.org/doi/full/10.1056/NEJMoa1707447

Summary

Background

In a phase 1 trial, axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, showed efficacy in patients with refractory large B-cell lymphoma after the failure of conventional therapy.

Methods

In this multicenter, phase 2 trial, we enrolled 111 patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma who had refractory disease despite undergoing recommended prior therapy. Patients received a target dose of 2×10^6 anti-CD19 CAR T cells per kilogram of body weight after receiving a conditioning regimen of low-dose cyclophosphamide and fludarabine. The primary end point was the rate of objective response (calculated as the combined rates of complete response and partial response). Secondary end points included overall survival, safety, and biomarker assessments.

Results

Among the 111 patients who were enrolled, axi-cel was successfully manufactured for 110 (99%) and administered to 101 (91%). The objective response rate was 82%, and the complete response rate was 54%.With a median follow-up of 15.4 months, 42% of the patients continued to have a response, with 40% continuing to have a complete response. The overall rate of survival at 18 months was 52%. The most common adverse events of grade 3 or higher during treatment were neutropenia (in 78% of the patients), anemia (in 43%), and thrombocytopenia (in 38%). Grade 3 or higher cytokine release syndrome and neurologic events occurred in 13% and 28% of the patients, respectively. Three of the patients died during treatment. Higher CAR T-cell levels in blood were associated with response.

Conclusions

In this multicenter study, patients with refractory large B-cell lymphoma who received CAR T-cell therapy with axi-cel had high levels of durable response, with a safety profile that included myelosuppression, the cytokine release syndrome, and neurologic events.

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

Stephen J. Schuster, Jakub Svoboda, Elise A. Chong, et al.
N Engl J Med 2017; 377: 2545-2554 December 28, 2017
http://www.nejm.org/doi/full/10.1056/NEJMoa1708566

Summary

Background

Patients with diffuse large B-cell lymphoma or follicular lymphoma that is refractory to or that relapses after immunochemotherapy and transplantation have a poor prognosis. High response rates have been reported with the use of T cells modified by chimeric antigen receptor (CAR) that target CD19 in B-cell cancers, although data regarding B-cell lymphomas are limited.

Methods

We used autologous T cells that express a CD19-directed CAR (CTL019) to treat patients with diffuse large B-cell lymphoma or follicular lymphoma that had relapsed or was refractory to previous treatments. Patients were monitored for response to treatment, toxic effects, the expansion and persistence of CTL019 cells in vivo, and immune recovery.

Results

A total of 28 adult patients with lymphoma received CTL019 cells, and 18 of 28 had a response (64%; 95% confidence interval [CI], 44 to 81). Complete remission occurred in 6 of 14 patients with diffuse large B-cell lymphoma (43%; 95% CI, 18 to 71) and 10 of 14 patients with follicular lymphoma (71%; 95% CI, 42 to 92). CTL019 cells proliferated in vivo

and were detectable in the blood and bone marrow of patients who had a response and patients who did not have a response. Sustained remissions were achieved, and at a median follow-up of 28.6 months, 86% of patients with diffuse large B-cell lymphoma who had a response (95% CI, 33 to 98) and 89% of patients with follicular lymphoma who had a response (95% CI, 43 to 98) had maintained the response. Severe cytokine-release syndrome occurred in 5 patients (18%). Serious encephalopathy occurred in 3 patients (11%); 2 cases were self-limiting and 1 case was fatal. All patients in complete remission by 6 months remained in remission at 7.7 to 37.9 months (median, 29.3 months) after induction, with a sustained reappearance of B cells in 8 of 16 patients and with improvement in levels of IgG in 4 of 10 patients and of IgM in 6 of 10 patients at 6 months or later and in levels of IgA in 3 of 10 patients at 18 months or later.

Conclusions

CTL019 cells can be effective in the treatment of relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma. High rates of durable remission were observed, with recovery of B cells and immunoglobulins in some patients. Transient encephalopathy developed in approximately one in three patients and severe cytokine-release syndrome developed in one in five patients.

Safety of Magnetic Resonance Imaging in Patients with Cardiac Devices

Saman Nazarian, Rozann Hansford, Amir A. Rahsepar, et al.

N Engl J Med 2017; 377: 2555-2564 December 28, 2017
http://www.nejm.org/doi/full/10.1056/NEJMoa1604267

Summary

Background

Patients who have pacemakers or defibrillators are often denied the opportunity to undergo magnetic resonance imaging (MRI) because of safety concerns, unless the devices meet certain criteria specified by the Food and Drug Administration (termed “MRI-conditional” devices).

Methods

We performed a prospective, nonrandomized study to assess the safety of MRI at a magnetic field strength of 1.5 Tesla in 1509 patients who had a pacemaker (58%) or an implantable cardioverter–defibrillator (42%) that was not considered to be MRI-conditional (termed a “legacy” device). Overall, the patients underwent 2103 thoracic and nonthoracic MRI examinations that were deemed to be clinically necessary. The pacing mode was changed to asynchronous mode for pacing-dependent patients and to demand mode for other patients. Tachyarrhythmia functions were disabled. Outcome assessments included adverse events and changes in the variables that indicate lead and generator function and interaction with surrounding tissue (device parameters).

Results

No long-term clinically significant adverse events were reported. In nine MRI examinations (0.4%; 95% confidence interval, 0.2 to 0.7), the patient’s device reset to a backup mode. The reset was transient in eight of the nine examinations. In one case, a pacemaker with less than 1 month left of battery life reset to ventricular inhibited pacing and could not be reprogrammed; the device was subsequently replaced. The most common notable change in device parameters (>50% change from baseline) immediately after MRI was a decrease in P-wave amplitude, which occurred in 1% of the patients. At long-term follow-up (results of which were available for 63% of the patients), the most common notable changes from baseline were decreases in P-wave amplitude (in 4% of the patients), increases in atrial capture threshold (4%), increases in right ventricular capture threshold (4%), and

increases in left ventricular capture threshold (3%). The observed changes in lead parameters were not clinically significant and did not require device revision or reprogramming.

Conclusions

We evaluated the safety of MRI, performed with the use of a prespecified safety protocol, in 1509 patients who had a legacy pacemaker or a legacy implantable cardioverter–defibrillator system. No long-term clinically significant adverse events were reported.

Back to Contents

Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
JAMA: The Journal of the American Medical Association	http://jama.ama-assn.org/
The Lancet	www.thelancet.com
The New England Journal of Medicine	http://content.nejm.org/
The British Medical Journal (BMJ), JAMA and the New England Journal of Medicine (NEJM) can be accessed in full-text through your NHS Athens account. Unfortunately the national subscription to The Lancet has been cancelled.	https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases or http://www.openathens.net/
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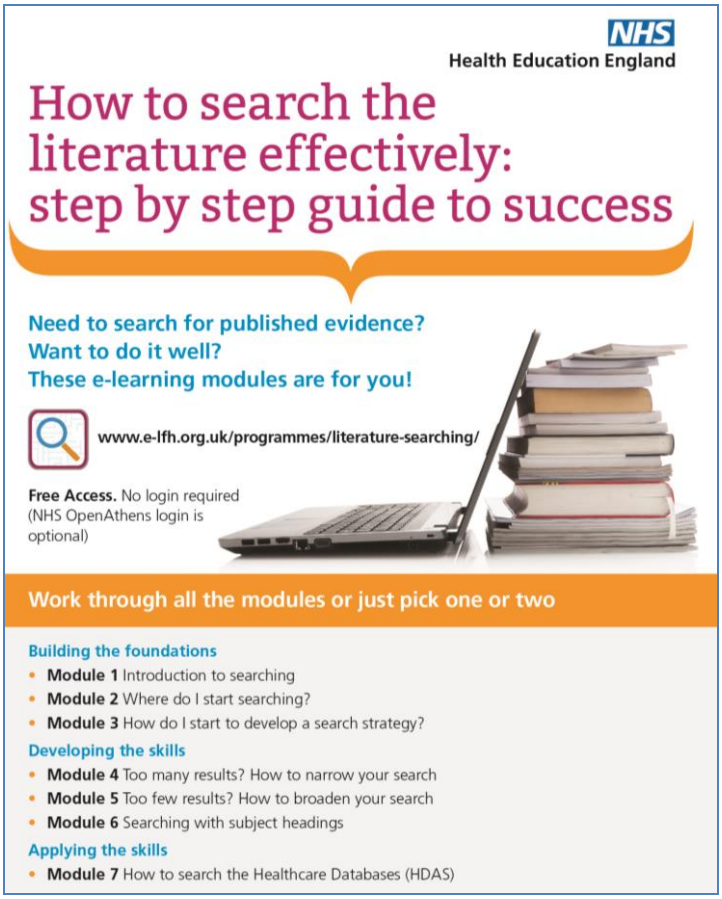

Library Training Sessions

Winter 2017/2018

- **JANUARY**

Using Evidence-Based Databases – *please book in advance*
Wednesday 17th 2:00pm — 3:00pm Library IT Room

Critical Appraisal (RCT paper) – *please book in advance*
Thursday 25th 2:00pm — 3:30pm Library Seminar Room 1

- **FEBRUARY**

Reflective Writing (for NMC Revalidation) – *please book in advance*
Thursday 8th 1:00pm — 2:00pm Library Seminar Room 1

Using Evidence-Based Databases – *please book in advance*
Friday 16th 1:00pm — 2:00pm Library IT Room

Critical Appraisal (Qualitative Study paper) – *please book in advance*
Tuesday 20th 2:00pm — 3:30pm Library Seminar Room 1

- **MARCH**

Undertaking RCT Research: study design basics and critical appraisal
Tuesday 6th 2:30pm — 4:00pm Library Seminar Room 1

Reflective Writing (for NMC Revalidation) – *please book in advance*
Friday 9th 12:00pm — 1:00pm Library Seminar Room 1

Using Evidence-Based Databases – *please book in advance*
Thursday 15th 12:00pm — 1:00pm Library IT Room

Critical Appraisal (Cohort Study paper) – *please book in advance*
Tuesday 20th 10:30am — 12:00pm Library Seminar Room 1

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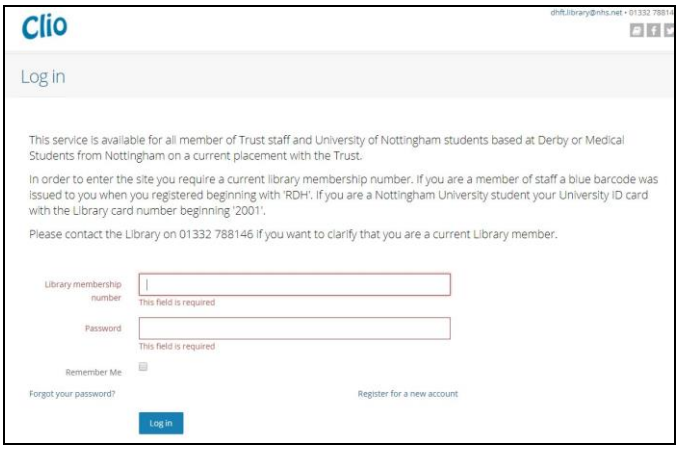

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