

<b>Institution:</b> University of Birmingham		
<b>Unit of Assessment:</b> UoA 1, Clinical Medicine		
<b>Title of case study:</b> Transformative Care for Idiopathic Intracranial Hypertension		
<b>Period when the underpinning research was undertaken:</b> 2010–2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Alexandra Sinclair	NIHR Lecturer NIHR Clinician Scientist Professor of Neurology	2010–2013 2013–2018 2019–present
<b>Period when the claimed impact occurred:</b> 2016–present		
<b>Is this case study continued from a case study submitted in 2014?</b> No		
<b>1. Summary of the impact</b>  <p>Research at the University of Birmingham has improved the management of patients with Idiopathic Intracranial Hypertension (IIH) by achieving the following:</p> <ol style="list-style-type: none"> <li><b>Improved patient outcomes</b>, including reducing episodes of blindness, fewer lumbar punctures, surgical procedures and hospital admissions;</li> <li><b>Development of the first International and European clinical guidelines for IIH</b>;</li> <li><b>International change in clinical practice for the management of IIH patients</b>;</li> <li><b>Creation of a spin-out company</b> to bring new drugs to patients.</li> </ol>		
<b>2. Underpinning research</b>  <p>Idiopathic intracranial hypertension (IIH) is a condition of unknown aetiology characterised by raised intracranial pressure (ICP). It is a disease of socioeconomic deprivation mainly affecting obese young women (95% of cases) and causing severe disabling headaches which reduce quality of life and can ultimately lead to blindness. The incidence of IIH has risen rapidly and is currently estimated to be 1 in 20,000, a 100% increase in the last decade, rising in line with global obesity. This has resulted in a 446% increase in associated UK hospital costs, with hospital economic burden rising from £9.2M in 2002 to £49.9M in 2014 [S1].</p> <p>Current therapies for IIH have poor efficacy and tolerability, and 48% of patients discontinue treatment. There are currently no targeted treatments to prevent blindness or severe disabling headache and, lacking an evidence base, international patient management strategies are highly variable. These factors have combined to perpetuate poor outcomes for patients — 25% of patients will have permanent visual loss as a result of optic disc swelling and the majority having chronic disabling headaches. High intracranial pressure is usually diagnosed by performing a lumbar puncture. This procedure also acts as an important treatment although some patients require neurosurgery with intraventricular shunt insertion to release the pressure.</p> <p>Although the vast majority of patients with IIH are obese, there was previously a lack of firm evidence that weight loss improved the condition. Sinclair developed a cohort of 25 women with active, chronic (over three months) IIH and identified <b>that 15% weight loss led to disease remission</b>, as evidenced by a <b>significant reduction in ICP</b> and <b>optic disc swelling (papilloedema)</b> measured by optical coherence tomography (OCT) [R1].</p> <p>In a further study, Sinclair then demonstrated for the first time that the use of OCT <b>to monitor papilloedema was beneficial</b> in clinical practice as an effective surrogate for raised ICP [R2]. For patients with sight-threatening IIH, neurosurgical shunting procedures are performed to</p>		

prevent blindness. However, there was previously no guidance to determine when this procedure should be undertaken, leading to many unnecessary surgical interventions. Sinclair reported on many potentially life-changing complications as a result of surgery, including blockage (12%), disconnection (7%) and infection (8%) with 51% of shunts failing and needing revision surgery within a year. The study concluded that **shunt surgery should only be performed to preserve rapidly declining vision**, and was not appropriate in other settings which could be managed medically, indicating that clinical practice needed to change [R3].

In a patient and physician research partnership, Sinclair also identified that patients were experiencing significant complications from lumbar punctures, including severe pain (40%) and extreme anxiety (47%) [R4, [Patient experience of lumbar puncture](#)] and furthermore illustrated **lack of efficacy** with headache exacerbation in 64%. The study concluded that performing repeated lumbar punctures in IIH should stop [R5].

There are no licenced drugs to treat IIH. Sinclair identified the **therapeutic potential of exenatide a glucagon-like peptide 1 receptor agonist to reduce ICP**, through its ability to reduce brain fluid production in animal models [R6]. The magnitude of effect is greater than any other drugs used in IIH. Exenatide is currently used for other conditions, and induces significant weight loss, a known disease modifier in IIH. Sinclair then performed a randomised placebo controlled trial in patients with IIH which demonstrated an acute (24 hours) and sustained significant reduction in ICP which was maintained for 12 weeks of dosing (Presented to the 14<sup>th</sup> European Headache Federation Congress in 2019. Abstract in Journal of Headache and Pain 2021 in press).

Key findings from the research are summarised below:

- KF1.** Weight loss leads to remission of IIH [R1];
- KF2.** Optical coherence tomography is beneficial to disease monitoring [R2];
- KF3.** Shunt surgery in IIH should only be conducted to preserve vision [R3];
- KF4.** Lack of efficacy of Lumbar puncture (LPs) in managing IIH [R4, R5];
- KF5.** The glucagon-like peptide 1 receptor agonist (Exenatide) is a novel drug strategy to reduce ICP and to treat IIH [R6].

### 3. References to the research

- R1. Sinclair AJ**, Burdon MA, Nightingale PG, Ball AK, Good P, Matthews TD, Jacks A, Lawden M, Clarke CE, Stewart PM, Walker EA, Tomlinson JW, Rauz S. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. *BMJ*. 2010 Jul 7;341:c2701. DOI: [10.1136/bmj.c2701](#)
- R2.** Vijay V, Mollan S, Mitchell J, Bilton E, Alimajstorovic Z, Markey K, Fong A, Walker J, Lyons H, Yiangou A, Tsermoulas G, Brock K, **Sinclair A**. Using Optical Coherence Tomography as a Surrogate of Measurements of Intracranial Pressure in Idiopathic Intracranial Hypertension. *JAMA Ophthalmology*. 2020 Dec 1;138(12):1264-1271. DOI: [10.1001/jamaophthalmol.2020.4242](#)
- R3. Sinclair AJ**, Kuruvath S, Sen D, Nightingale PG, Burdon MA, Flint G. Is cerebrospinal fluid shunting in idiopathic intracranial hypertension worthwhile? A 10-year review. *Cephalalgia*. 2011 Dec;31(16):1627-33. DOI: [10.1177/0333102411423305](#)
- R4.** Scotton W, Mollan S, Walters T, Doughty S, Nightingale P, Botfield H, Markey K, Yiangou A, Williamson S, **Sinclair AJ**. Characterising the patients experience of diagnostic lumbar puncture in idiopathic intracranial hypertension; a cross-sectional online survey. *BMJ Open* 2018 May 30;8(5):e020445. DOI: [10.1136/bmjopen-2017-020445](#)
- R5.** Yiangou A, Mitchell J, Markey KA, Scotton W, Nightingale P, Botfield H, Ottridge R, Mollan S, **Sinclair AJ**. Therapeutic Lumbar Puncture for headache in Idiopathic Intracranial Hypertension: minimal gain, is it worth the pain? *Cephalalgia* 2018 Jan 1;333102418782192. DOI: [10.1177/0333102418782192](#)
- R6.** Botfield HF, Uldall MS, Westgate CSJ, Mitchell JL, Hagen SM, Gonzalez AM, Hodson DJ, Jensen RH, **Sinclair AJ**. A glucagon-like peptide-1 receptor agonist reduces

intracranial pressure in a rat model of hydrocephalus. *Sci Transl Med*. 2017 Aug 23;9(404). DOI: 10.1126/scitranslmed.aan0972

#### 4. Details of the impact

The management and treatment of patients with IIH has been shaped by Sinclair's research in four key ways.

##### 1. Improved outcomes and understanding for patients with IIH

Evaluation of UK Health Episodes Statistics data shows the following patient outcomes have improved:

- **Reduction in IIH patients registered blind** — from 2.1% prior to 2018 to 1.4% in 2019 [S1]. This benefit stems from the adoption of OCT imaging [R2; KF2] into practice, which “helps to guide on which patients need shunt surgery to prevent blindness” (S4).
- **Reduced hospital admissions as a result of reductions in lumbar punctures and shunt procedures** [S1]:
  - Shunting levels were consistently high prior to 2018 but have markedly fallen since, from 8.3% (2002–2016 [S1]) of IIH patients to 3.1% (2018–2019, [S1]);
  - Shunt revision rates falling from 2.8% to 0.6%, reflecting revision of shunt for visual issues/visual failure only [S1];
  - The proportion of patients requiring re-admissions for IIH, within one year of diagnosis, has also decreased from 38% (2002–2016) to 35% (2018–2019), whilst reductions in the proportions of patients requiring >2 admissions to hospital per year has fallen from 11.9% (2002–2016) to 9.3% (2018–2019), [S1]. These data reflect a reduction in attendance for repeated lumbar puncture and shunt surgery.
- Patients can now make more **informed treatment decisions**. For example, it is now clear that weight loss is an important form of disease management and an approach to avoid harmful therapies, such as lumbar punctures and shunt surgery [R2, R3]. Evidence that patient knowledge and understanding has markedly improved was demonstrated in spring 2020 using E-surveys to patients (465 UK respondents and 115 international respondents). These documented that patients' understanding of optimal care has been enhanced [S2] with:
  - 99% of respondents now aware of the link between body weight and IIH;
  - 89% aware that surgery should be reserved for people losing vision;
  - 71% aware that there was a limited medical role for LPs.

Sinclair reinforced these messages through her role as Patron of the National IIH charity, where patient education was delivered through Question and Answer videos, patient conferences and patient information leaflets published on the charity website [S3i–ii].

##### 2. Development of the first International clinical guidelines to shape IIH patient care and improve patient management

Sinclair led development of the **first international guidelines for IIH** [S4i–iv], published in 2018. Prior to this, there was no standardised care for management of IIH and practices varied widely around the globe. Sinclair was then commissioned to **produce the European Headache Federation IIH guideline** [S4ii] (2018). Recommendations include:

- (i) “Primary principle for IIH management: modify the underlying disease through weight loss” [S4i, page 1092; S4ii, page 10; R1];
- (ii) That OCT should be introduced for objective monitoring of papilloedema [S4i, page 1090; S4ii, page 3; R2];

- (iii) That shunting surgery should only be conducted to preserve vision [S4i, page 1093–4; S4ii, page 7–8; R3], and make firm recommendations to change practice in patient management;
- (iv) That “Serial lumbar punctures are not recommended for management of IIH” [S4i, page 1095; S4ii, page 11; R4, R5).

### 3. International change in clinical practice for the management of IIH patients

Patient care practices and services have been redesigned both nationally and internationally, in line with the service set up by Sinclair at the University of Birmingham (the largest in Europe). Clinical practice has changed in three key ways:

- (i) **Pathways for weight loss have been introduced** [R1; KF1]. The percentage of patients with recorded weight counselling has risen since 2018 [S1]. Data from the patient e-survey indicated that >50% of patients felt the guidelines had helped doctors to improve their care, in key areas such as weight management [S2].
- (ii) **OCT has been introduced for objective monitoring of papilloedema** [R2; KF2]. That this is the case is confirmed by Professor of Neurology at the Danish Headache Center University of Copenhagen (2021, [S5]) who states “These changes to patient care, detailed in the IIH guidelines, have led to redesign of routine care pathways globally to improve patient outcomes. Internationally we have adopted the use of OCT image to monitor papilloedema in clinics. This has had the benefits of reducing the need for painful LPs and helps to guide on which patients need shunt surgery to prevent blindness” [S1].
- (iii) **Collaborative working takes place between multiple specialities.** A multidisciplinary team approach bringing together neurology, ophthalmology, neurosurgery and dietetics has been adopted to allow the correct selection of patients for shunt surgery [R3; KF3]. This approach was identified as important during the James Lind Priority setting Partnership 2018 “multidisciplinary clinics were scored as important” [page 4, S6] and change is evidenced by a reduction in shunt procedures and reduced shunt revisions, alongside reduced rates of blindness seen in patients [S1]. International change is further attested to by Professor of Neurology at the Danish Headache Center University of Copenhagen (2021) who states “The change in practice to bring together neurologists, ophthalmologists, and neurosurgeons to work more closely together in a multi-specialty team has dramatically improved patient care and outcomes and is now a core principle of IIH clinical pathways”.

### 4. Bringing new drugs to patients through the creation of a University of Birmingham spin-out company

Significant commercial impact has stemmed from Sinclair’s findings that exenatide can reduce ICP [R6; KF5]. Working with University of Birmingham Enterprise Sinclair has:

- Secured intellectual property through filing and the granting of a method of use patent;
- Obtained orphan drug designation (ODD) granted by the FDA and European Medicines Agency (2017) [S7i];
- Undertaken a proof of concept clinical trial that has culminated in raising significant funding (round 1 \$AU12M + round 2 \$AU26M) to create a University of Birmingham spin-out company, Invex Therapeutics [S7ii] to repurpose exenatide specifically for IIH [S7iii]. The company was launched on the Australian Stock market in July 2019 [S7iv–v] and current value (19/11/2020) was Market cap value £29.9M, Enterprise value £15.5M, revenue £91.3k and share value of \$AU0.8 [S7vi]. The company is about to initiate manufacture of the drug Presendin (reformulated to specifically control ICP) which will be used in a phase 1 and a large phase 3 international randomised controlled trial in IIH [S7ii]. Sinclair is working with the FDA and EMA to file an investigational new drug application (IND) and establish trials to enable market authorisation and licencing of the drug for IIH patients. This will be the first licenced drug for IIH and a step-change in improving patient care.

## 5. Sources to corroborate the impact

**S1.** The survey of Hospital Episode Statistics Data analysed 2020, illustrating change in practice and patient benefit post publication of guidelines.

**S2.** Patient e-survey (carried out through IIHUK Patient Charity to 5,230 social media followers UK and international, October/November 2020), illustrating increased knowledge of patients and better-informed decision on their care, leading to improvements in patient care.

**S3.** Patient education to make informed decision about their care is evidenced by the patient education (i) [videos](#) and information; (ii) [sheets](#) on the IIHUK website.

**S4. (i)** Idiopathic intracranial hypertension consensus guidelines on management. Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, Krishnan A, Chavda SV, Ramalingam S, Edwards J, Hemmings K, Williamson M, Burdon MA, Hassan-Smith G, Digre K, Liu GT, Jensen RH, Sinclair AJ. *J Neurol Neurosurg Psychiatry*. 2018 Oct;89(10):1088-1100. DOI: 10.1136/jnnp-2017-317440; (ii) European headache federation guideline on idiopathic intracranial hypertension. Jan Hoffmann<sup>1</sup>, Susan P Mollan<sup>2</sup>, Koen Paemeleire<sup>3</sup>, Christian Lampl<sup>4</sup>, Rigmor H Jensen<sup>5</sup>, Alexandra J Sinclair *J Headache Pain*. 2018 Oct 8;19(1):93. DOI: 10.1186/s10194-018-0919-2; (iii) [infogram](#) and (iv) [podcast](#)

**S5.** Testimonial from President of International Headache Society and Professor of Neurology at the Danish Headache Center University of Copenhagen (23/01/2021), supporting adoption of University of Birmingham exemplar service structure as developed in response to research and guidelines.

**S6.** The patients and physicians top 10 research priorities setting partnership (James Lind Association) which highlighted gaps in doctor and patient education as well as areas in need of future research ([BMJ Open 2019](#)).

**S7. (i)** Patenting and obtaining orphan drug designation (ODD); (ii) [invextherapeutics](#) and (iii) Repurpose of Exenatide for IIH, (iv) and (v) Floatation of company of the Australian stock market July 2019, (vi) Confirmation of stock market value (19/11/2020).