Planning interventional trials in childhood arterial ischaemic stroke using a Delphi consensus process

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ABSTRACT

Background: There is paucity of data from randomised controlled treatment trials in childhood arterial ischaemic stroke. Our objectives were to identify and plan a trial through use of a Delphi consensus process.

Methods: The Delphi panel consisted of Australian, New Zealand and European paediatric neurologists with an interest in childhood stroke. Four rounds were conducted using a REDCap web based application; the first consisted of open ended questions, the second evaluated agreement for the most important trial, and the third and fourth reached consensus on design.

Results: 47/66 neurologists answered the first round. Eight areas of research for important and feasible trials were identified. In the second round 43 ranked the 3 highest rated trials: Aspirin versus aspirin plus steroids in focal arteriopathy (n=31), (ii) heparin versus aspirin (n=6) and (iii) heparin versus aspirin versus modern anticoagulation (trial 3n=6). The third and fourth surveys reached consensus among 43/44 respondents on design of the highest ranked trial, and allowed agreement on inclusion / exclusion criteria, clinical / neuroimaging data and treatment protocols.

Conclusion: The Delphi Consensus Process is an efficient method of identifying and planning paediatric stroke trials. An international multicentre trial is now in preparation.

What this paper adds:

- Example of a Delphi process to evaluate research questions and design for a research protocol
- Most important and feasible study evaluated: Steroid Aspirin versus Aspirin alone in focal arteriopathies in childhood stroke
- Suggestions on a design for such a study
- Information on current treatment decisions in Europe and Australia/New Zealand

Keywords
Delphi consensus; childhood arterial ischaemic stroke; focal cerebral arteriopathy; treatment trial; steroid; aspirin
INTRODUCTION

Childhood arterial ischaemic stroke (AIS) affects 1.6-2.12 per 100,000 children per year\(^1\). There is a total burden for neonatal and childhood AIS of almost 100’000 children per year worldwide \(^2\). There is almost complete lack of evidence concerning acute and secondary preventative treatment of childhood stroke, which is reflected by consensus based recommendations in guidelines\(^3\). Extrapolating treatment recommendations from adults may not be appropriate due to differences in stroke pathogenesis, most notably the absence of risk factors for atherosclerosis in children\(^4\).

Mortality ranges from 7–28%, with death being caused by the stroke or the underlying disease\(^1,4\). There are high rates of morbidity in survivors with 50% of children having neurological deficits \(^5\) and even higher rates of cognitive deficits\(^6\). Refining management of childhood stroke, based on evidence, therefore seems mandatory to minimise long term sequelae. The relative infrequency of childhood AIS necessitates multicentre international collaboration but there are substantial obstacles to conducting such trials.

Planning interventional studies requires health professionals to agree and prioritise studies of highest clinical importance. The aims of the study were therefore, to identify the most important treatment trial, by conducting a Delphi consensus process among paediatric neurologists, and determine the most feasible study design across sites, based on majority agreement.

The Delphi Consensus Process, developed in the 1950’s for forecasting technological developments, \(^7\)explores opinions among groups of people with common interests and experience. It is increasingly used in health care settings to reach agreement among clinicians \(^8\) and lay persons\(^9\). Agreement is reached following two to four iterative questionnaires. Ten to 30 participants are considered adequate to produce reliable results.\(^10\)
METHODS

Participants were identified by searching Pubmed for corresponding authors of publications related to childhood stroke, and/or by their participation in a national/regional paediatric stroke network within Europe, Australia and New Zealand. Participants were contacted by email for the first round and asked whether they would be willing to participate in the Delphi process.

There were two iterative rounds of questionnaires to reach consensus about the most important and feasible trial, followed by two rounds to design the trial (see supplemental information). A survey was also conducted of current diagnostic and treatment practice at participating institutions.

Survey data were collected and managed using the REDCap (Research Electronic Data Capture) tools, a secure, web-based application designed to support data capture for research studies11.

The first open questionnaire (supplemental information) asked participants to separately list the five most important and five most feasible clinical treatment trials. A feasibility score (5 points most feasible) was calculated. The second questionnaire (supplemental information) summarised results from the first questionnaire and asked participants to rank the three highest scoring trials from the first round, in terms of importance and feasibility. Participants were also asked about (i) willingness to enrol patients in the three study proposals, if the protocol deviated from normal clinical practice, and an optional choice (ii) of potential primary and secondary outcomes of interest for each trial. Specific outcomes offered included clinical or radiological recurrence, outcome at 6 weeks or 6 months, evolution of vasculopathy or other outcome (free text). Finally, demographic data was collected on survey participants.

Once consensus was achieved about the most important trial, input for a third and fourth survey was sought from specialists in other disciplines
relevant to the proposed trial (immunologists, endocrinologists, infection disease specialists, neuroradiologists, clinical trialists and biostatisticians).

The third round summarised results of the second round. This was followed by questions to reach consensus on definition of focal cerebral arteriopathy and the most pragmatic study design across sites, including survey of current practice, inclusion/exclusion criteria, clinical data elements to be collected, minimal imaging requirements for diagnosis, treatment regimes, follow up imaging protocols, study end points and primary and secondary outcome measures (supplemental information). The fourth round followed on questions about inclusion time to study entrance and acyclovir treatment in the steroid arm (supplemental information). For the purposes of analysis major agreement was defined as 90% consensus, minimum agreement was defined as 80% consensus.

RESULTS

Sixty six potential survey participants were identified, of whom 47 answered the first round of questions (42 the second, 43 the third and 44 the fourth round); three declined involvement, email contact addresses for eight participants were incorrect and further contact was not possible. A further eight did not respond for unknown reasons. All except two participants were neuropaediatricians, balanced for gender and age; 31/43 were working mainly in clinical practice and 12/43 as academic clinicians. Three quarters were involved in research and had experience with interventional trials. 48 answered at least two of the questionnaires: seven respondents had been first/senior authors on research papers about childhood stroke, another 14 had been first/senior authors on relevant research papers, and the remaining 27 were integrated into paediatric stroke networks (many co-authors on relevant research papers).

The First Delphi Round

Results of the first Delphi round are summarised in table 1. Trials focusing on childhood stroke were identified by 38 of participants. A few identified
neonatal AIS and sinus venous thrombosis (SVT) trials as being important. Other suggested trials for childhood stroke included long term secondary prevention in childhood stroke, treatment of epilepsy, heparinisation for SVT, general treatment approaches in neonatal stroke and effect of physiotherapy. There were additional suggestions concerning risk factors, genetics, and diagnostic approaches. One participant, who declined further involvement, was concerned about insufficient knowledge of childhood AIS pathophysiology to warrant treatment trials.

**The second Delphi round**

The second round questionnaire explored the most important and feasible studies identified by the first survey. Participants were asked to rank the three highest scoring trials from the first survey. 43 participants responded to the second questionnaire, but only 42 answers were available for some questions. A trial comparing aspirin plus corticosteroids, versus aspirin treatment alone, for stroke in focal cerebral arteriopathy (FCA) was identified as the most important and feasible trial (table 2).

Willingness to include children in the trials, even if it deviated from normal clinical practice also favoured the aspirin and steroids versus aspirin trial (table 2). Fewer participants were willing to randomise patients to trials of antiplatelet versus anticoagulant therapy, prior to exclusion of cardiac and or dissection (14 and 18 participants respectively).

There were four options for possible primary and secondary outcomes. Survey answers provided by 30 to 42 of participants about possible primary and secondary outcome are summarized in table 3. The required 80% level of consensus was not achieved for outcomes but there was greater than 50% agreement found for each trial (table 3).

Demographic information on survey participants is summarised in table 4.

**The third Delphi round**
The second survey suggested that a trial comparing aspirin to aspirin plus steroids in children with FCA had the highest ratings in terms of importance, feasibility and willingness to participate. The focus of the third survey was therefore to determine current practice across sites, diagnostic definitions, baseline variables, outcomes of interest, and key requirements for conducting the trial.

More than 90% consensus (agreement from at least 40/44 participants) was reached in the following areas.

**Study inclusion criteria and definition of FCA:** (i) unilateral focal arteriopathy in ≤ 2 vessels affected with irregularity and/or stenosis, or occlusion on vascular imaging, (ii) acute infarction in the area of at least one affected vessel, (ii) age at stroke 6 months-18 years, (iii) no evidence of an underlying systemic disorder, (iv) informed consent obtained from parents.

**Study exclusion criteria:** (i) secondary CNS angiitis, due to infections (meningitis, encephalitis), rheumatic or other systemic inflammatory disease, (ii) progressive large to medium vessel in childhood primary angiitis of the central nervous system (cPACNS), (iii) already on steroid treatment at presentation, (iv) congenital or acquired immunodeficiency and (iv) Moyamoya disease or syndrome.

**Presenting clinical variables to be collected:** (i) medical history and neurological findings (using a predetermined case report form), (ii) vital observations as bodyweight, temperature, blood pressure, and (iii) stroke severity, using the pediatric NIH stroke score (pedNIHss).

**Minimal diagnostic imaging requirements prior to inclusion and at follow up:** (i) diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps, (ii) axial fluid attenuated inversion recovery (FLAIR), (iii) susceptibility weighted imaging (SWI) and (iv) arterial 3D time of flight (TOF) magnetic resonance (MRA) vascular imaging.
**Treatment regimen for study patients:** (i) aspirin or heparin treatment before enrolment to the study (on individual clinical decision), with inclusion into study: (ii) both treatment arms to receive 5mg/kg bodyweight (BW) aspirin daily (max 300mg/day), (iii) 5 days pulse of 20mg/kg BW methylprednisolone (max 1g/day) for steroid arm, (iv) followed by a six-week tapering regime using oral prednisolone and (v) no need for stress test (assessing the pituitary adrenal axes) following tapering of steroids.

More than 80% consensus (agreement from at least 35 participants) was reached for two questions. Thirty-nine agreed to *enrolment within 4 days* of admission; two suggested less than 4 days and two more than 4 days. Thirty-six participants agreed to first *follow up imaging* at three months, one suggested imaging at one month, and six at six months only.

Consensus could not be reached for acyclovir treatment. Thirty (68%) participants felt that acyclovir was indicated prior to exclusion of varicella infection (positive CSF VZV PCR or antibodies, or serum IgM antibodies) in children with a history of exposure within six month prior to stroke diagnosis.

The survey of current treatment practice for FCA revealed that all children were treated with corticosteroids in 9 centres (20%). Usage was a treatment option in the remaining 32 centres; corticosteroids were used if there were ongoing TIAs or recurrent strokes, despite aspirin in 21 centres, or in cases with radiological or sonographic worsening of FCA in 30 centres. Eleven participants raised concerns that corticosteroid side effects may outweigh potential benefits. Vessel wall imaging was used to guide usage of corticosteroids at 26 centres. Acyclovir was used in combination with steroids in children with FCA at only 8 centres, whereas 31 centres prescribed acyclovir in cases with VZV positivity on CSF examination and or serology. Unfortunately, the question of how positive history of varicella would influence this decision was not asked.

**The Fourth Delphi Round**
The fourth round was answered by 44 participants and reached majority agreement on reducing time to enrolment to 48 hours –two participants suggesting shorter, and two longer inclusion times. Consensus was also reached for use of acyclovir treatment in the steroid arm until exclusion of active infection by herpes and/varicella virus by PCR or antibodies in CSF and/or serum.

**DISCUSSION**

A study comparing aspirin plus corticosteroids to aspirin treatment alone was identified as the most important and feasible trial by the vast majority of respondents. Importantly the majority of respondents were also prepared to enrol patients even if this deviated from their normal clinical practice. Similar to the WEST Delphi that informed the design of the recently published ICISS trial investigating the treatment of infantile spasms\textsuperscript{12}, this Delphi process has provided useful information on current diagnostic protocols and treatment practice among a multinational group of paediatric neurologists, influencing the design of the proposed trial.

The varied response in the first open questionnaire highlights the current lack of evidence for treatment of childhood stroke. Thrombolysis and mechanical thrombectomy were felt to be the most important trials, probably explained by the strong evidence for efficacy in adults\textsuperscript{13,14}. However, there is great uncertainty about the efficacy of thrombolysis in childhood stroke because of the different aetiologies involved.

Respondents felt that trials of thrombolysis and thrombectomy were not feasible, possibly reflecting concerns regarding long lead-time to diagnosis of arterial ischaemic stroke in children\textsuperscript{15}. This is also reflected in the problems encountered by the TIPS trial, which despite preparing an in house emergency management protocol failed to recruit adequate numbers of patients\textsuperscript{16}.
A corticosteroid trial in FCA was identified as the most feasible and second most important trial. This was confirmed in the second round, with respondents willing to enrol subjects, even if the allocated treatment deviated from normal practice. Recent publications suggest an important role of inflammation and infection in childhood stroke. Herpes group viruses are the most common infectious agent in FCA, but there are other infectious triggers. Corticosteroids were already being used in the majority of centres by survey participants, although there was practice variation.

Trials of antiplatelet versus anticoagulant therapies were considered to be less important and feasible. There is evidence in adults, that antiplatelet therapy is superior to anticoagulation in acute ischaemic stroke. It is important to acknowledge, however, that arteriosclerosis, the major risk factor in adults is not a significant risk factor in children. Still, extrapolation of data on these treatment modalities to the childhood population is probably more reliable than for thrombolysis. In addition, trials of antiplatelet agents versus anticoagulants require large numbers to demonstrate a treatment effect.

The third survey focused on study design. There was ≥90% consensus for inclusion criteria, with the exception of lag time to study entry. Discussion between participants brought high consensus in a fourth round for enrolment within 48 hours, which balances the need for early implementation of steroid treatment to reduce vascular inflammation against the need of time to complete diagnostic investigations prior to inclusion. It is particularly important for clinicians to exclude cardioembolic stroke and arterial dissection, because consensus based paediatric stroke guidelines suggest anticoagulation as the treatment of choice in both conditions.
There was majority agreement for suggested exclusion criteria. The problem of recognising a progressive vasculopathy at initial presentation was discussed in free comments. For some conditions such as primary CNS angiitis, steroids are the treatment of choice. On the other hand the risk of steroids in non-inflammatory progressive arteriopathies such as Moyamoya, masquerading as a unilateral FCA were not rasied as a major concern. To decrease the risk even further, inclusion criteria were limited to unilateral FCA and additional secondary safety outcomes were chosen.

There was more than 90% consensus for a minimum neuroimaging dataset. DWI/ADC maps are considered the gold standard to identify ischaemic lesions\textsuperscript{21}, FLAIR images help determine timing of the lesion\textsuperscript{22}, SWI for detection of haemorrhage, and time of flight MR angiography to assess vessel status. Some participants indicated that advanced imaging (perfusion and vessel wall imaging) could be performed at their centres, which will be important for the development of satellite neuroimaging studies.

There was much discussion in the free text responses about the proposed treatment regimen, but once again majority agreement was reached in the third and fourth surveys for all questions. Aspirin dosage was chosen based on published consensus guidelines.\textsuperscript{3} Corticosteroid regimens and surveillance for side effects were chosen, based on dosage and formulation used in paediatric demyelinating and inflammatory disorders\textsuperscript{23}. Published data suggests that serious side effects are rare with short duration high dose steroid regimens\textsuperscript{24}. Expert advice from endocrinologists (FC) and neuroimmunologists (RD) agreed with the proposed treatment regime.

Consensus on acyclovir treatment in steroid arm was reached in the fourth Delphi round. Varicella virus has been detected in the vessel wall
in post varicella vasculopathy and the arteriopathy is thought to be related to a reactivation of the inflammatory process.\textsuperscript{25} The Vascular Infectious Pediatric Stroke Groups (VIPS) study, however, suggests that arteriopathy might also be related to a primary infection by herpes group viruses\textsuperscript{19}. A recent review on management of varicella arteriopathy \textsuperscript{26} and also our survey revealed that antiviral therapy is given increasingly in FCA.

There was only 80\% agreement for timing of follow-up imaging at 3 and 6 months respectively i.e. earlier imaging at 3 months to identify potential worsening versus 6 months only as a study endpoint. There were concerns that the protocol might entail extra anaesthesia in some children, but there is a strong argument that most of studies would be indicated clinically. Protocols on performing MR images without anaesthesia/sedation in children are available\textsuperscript{27}. Insisting on only a limited imaging data set will facilitate MR imaging.

Eight respondents suggested longer follow up than 6 months. However, recurrence and worsening of the arteriopathy peaks around 3 months after stroke\textsuperscript{18} and neurological outcome at 6 months has been shown to accurately reflect longterm outcome\textsuperscript{6}. Therefore, we believe a primary endpoint at 6 months with a secondary endpoint at 12 months is justified.

The feasibility of such a study depends on the willingness of clinicians to enrol patients. This Delphi survey suggests that 41/43 participants would be willing to include patients. Using time to recovery as the primary outcome and postulating an effect size of 0.5, a sample size calculation by a generic approach suggests that 128 children would be needed in a trial (90\% power, alphalevel of 0.05). Using known incidence data, we estimate to recruit 200 children over three years from five existing stroke networks in Europe/Australasia. Participation of other centres
would accelerate recruitment and possibly shorten the duration of any proposed trial.

This study has limitations. In particular there was a geographical bias. More centres from Great Britain, Switzerland and Australia were involved, which may reflect the presence of established paediatric stroke research networks but may also reflect the nationality of the authors. There were significantly more European than Australian participants, but this is likely explained by larger population in Europe than Australia. There were no participants from either North or South America and therefore the generalizability of the consensus views expressed here only applies to Europe and Australasia.

The Delphi process is a method of obtaining consensus among experts. The process will not, per se, determine the feasibility of a proposed study. However, obtaining consensus about definitions and possible study protocols will increase the likelihood of the success of any future trial and the acceptance of any results that the trial produces amongst the relevant expert community.

In conclusion, the Delphi consensus process is a feasible and valuable instrument to survey current practice and to engage paediatric neurologists in the design of a paediatric stroke treatment trial which is acceptable to clinical researchers. The Delphi suggests that a randomised trial comparing aspirin and steroids to aspirin alone is the most important, feasible and acceptable childhood AIS trial. More than 90% consensus was reached for almost all components of the proposed trial, increases the likelihood of successful completion.
Acknowledgments: We thank Christoph Aebi, Russel Dale, Marwan Elkoussy, Simone Mandelstem, Sven Trelle, for the input into the design of the study.
Reference list


## Tables

### Table 1: Most important clinical trials in arterial childhood stroke

<table>
<thead>
<tr>
<th>Topics of possible studies</th>
<th>Most important*</th>
<th>2nd most important*</th>
<th>3-5th important*</th>
<th>Feasibility **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppressive treatment in FCA</strong></td>
<td>9</td>
<td>4</td>
<td>6</td>
<td>3.89</td>
</tr>
<tr>
<td>Aspirin versus Heparin</td>
<td>3</td>
<td>12</td>
<td>13</td>
<td>3.25</td>
</tr>
<tr>
<td>Aspirin versus different anticoagulants</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>3.5</td>
</tr>
<tr>
<td>Thrombolysis (ia, iv)</td>
<td>17</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>2.3</td>
</tr>
<tr>
<td>Other Treatments</td>
<td>2</td>
<td>4</td>
<td>24</td>
<td>3.3</td>
</tr>
<tr>
<td>Non treatment trials in childhood AIS</td>
<td>2</td>
<td>4</td>
<td>15</td>
<td>3.69</td>
</tr>
<tr>
<td>Treatment in neonatal stroke and/or SVT</td>
<td>1</td>
<td>7</td>
<td>12</td>
<td>3.35</td>
</tr>
</tbody>
</table>

FCA focal cerebral arteriopathy. AIS arterial ischaemic stroke. SVT sinus venous thrombosis

* number of participants ranking the topic in this level

** Feasibility ranked by participants (ranking from 1-5: 5 being very feasible and 1 being unfeasible)
<table>
<thead>
<tr>
<th>Trial</th>
<th>most important</th>
<th>2nd most important</th>
<th>least important</th>
<th>willingness for inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin and steroids versus aspirin alone</td>
<td>31</td>
<td>5</td>
<td>7</td>
<td>41</td>
</tr>
<tr>
<td>(n=43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin versus Heparin (n=42)</td>
<td>6</td>
<td>19</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>Aspirin versus Heparin versus modern oral</td>
<td>6</td>
<td>19</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>AC (n=43)</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>
Table 3: Choices for primary and secondary outcomes

<table>
<thead>
<tr>
<th>Primary outcome /secondary outcome suggested for the 3 different trials</th>
<th>Aspirin / Aspirin - Steroids</th>
<th>Aspirin / Heparin</th>
<th>Aspirin / Heparin / modern AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical and/or radiological stroke recurrence within 6 weeks</td>
<td>13 /17</td>
<td>17/13</td>
<td>17 /13</td>
</tr>
<tr>
<td>Clinical and/or radiological stroke recurrence within 6 months</td>
<td>26 /16</td>
<td>18 /20</td>
<td>19 /20</td>
</tr>
<tr>
<td>Clinical outcome after 6 months</td>
<td>14 /23</td>
<td>12 /28</td>
<td>11 /27</td>
</tr>
<tr>
<td>Normalisation of vasculopathy</td>
<td>9 /27</td>
<td>6 /24</td>
<td>7 /23</td>
</tr>
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Table 4: Demographic information on survey participants

<table>
<thead>
<tr>
<th>Speciality</th>
<th>Neuropaediatrics</th>
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<td>2</td>
</tr>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Age groups</td>
<td>35-44 years</td>
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<tr>
<td></td>
<td>45-54 years</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>55-65 years</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>&gt; 65 years</td>
<td>1</td>
</tr>
<tr>
<td>Working place</td>
<td>Australia New Zealand</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>34</td>
</tr>
<tr>
<td>Working area</td>
<td>regional hospital</td>
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<tr>
<td></td>
<td>tertiary care hospital</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>university hospital</td>
<td>27</td>
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<tr>
<td>Working area</td>
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<tr>
<td></td>
<td>mainly research</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>mix</td>
<td>12</td>
</tr>
<tr>
<td>Involvement in research</td>
<td>currently</td>
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<tr>
<td></td>
<td>past /present participation in multicentre treatment trials</td>
<td>31</td>
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<tr>
<td>Position</td>
<td>training</td>
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<tr>
<td></td>
<td>staff member</td>
<td>25 (7 part time)</td>
</tr>
<tr>
<td></td>
<td>head of division</td>
<td>17</td>
</tr>
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Supplementum

Questionnaires 1-4 of Delphi Survey