The INTERnational Study on Primary Angiitis of the CEntral nervous system (INTERSPACE)

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INTRODUCTION

Primary (isolated) angiitis of the CNS (PACNS) = real diagnostic and therapeutic challenges

Diagnostic challenges
- **Rarer than several other potential mimickers**
- **No individual clinical manifestation or non-invasive test result is specific**
- **Diagnosis often presumed from a combination of manifestations and test results otherwise unexplained**
- **CNS biopsy can confirm PACNS, but invasive and ≥30% false-negatives**
- **Several patients remain with a presumptive diagnosis of PACNS**

INTRODUCTION

Therapeutic challenges

• **Optimal therapeutic regimen and duration are unknown for PACNS in general and for specific subgroups**

Risk of adverse effects of immunosuppressant agents

Risk of treatment failure due to insufficient treatment

• **Monitoring of therapeutic response can be difficult**
• **Predictors of treatment failure and recurrent PACNS are unknown**

INTERSPACE

Design: Observational prospective multicentre study on PACNS

Funding: Unrestricted grant from *La Fondation des Gouverneurs de l'Espoir*

INTERSPACE

Primary objective: Predictors of death or dependence (mRS 3 to 6) at the end of follow-up

    Sample size calculation: Assuming death or dependence in 30% of the study population, 200 participants are necessary to identify and integrate 6 predictors to a multivariate model

INTERSPACE: Secondary objectives

1) Predictors of death or dependence 1 year following initiation of immunosuppressive therapy

2) Predictors of neurological deterioration due to treatment failure (>14 days after initiation of immunosuppressive therapy) or recurrent PACNS (following discontinuation of immunosuppressive therapy), defined by the combination of:

- **Clinical manifestations of active vasculitis**
- **Investigation results consistent with active vasculitis**

3) Long-term outcome (>1 year following initiation of immunosuppressive therapy)

4) Recognizable subsets of PACNS with specific clinical manifestations, investigation results, or outcomes

INTERSPACE: Tertiary objectives

Optional sub-studies with separate protocols:

1) Innovative brain and vascular imaging techniques (R Swartz, Toronto)

2) CSF biomarkers (R Geraldes, Lisbon)

3) Genetics (D Hunt, Edinburgh)

4) Incidence study (S Lanthier, Montreal)

5) Sensitivity of non-invasive investigations

6) Differential diagnosis of PACNS

7) PACNS revealed only at autopsy

INTERSPACE: Study subjects

Inclusion criteria

- Age ≥16 years
- Acquired neurological dysfunction (headaches, cognitive decline, seizures and focal deficits) consistent with PACNS and unexplained by a long list of other causes
- A "high-probability" imaging study of the CNS vessels *OR* CNS histopathology confirming PACNS
- Exclusion of diseases that can mimic PACNS

Exclusion criteria:
- Immunosuppressive therapy initiated before obtaining brain or spinal cord MRI
- Immunosuppressive therapy initiated >30 days before study enrolment
- Consent form not obtained

INTERSPACE: Enrolment process
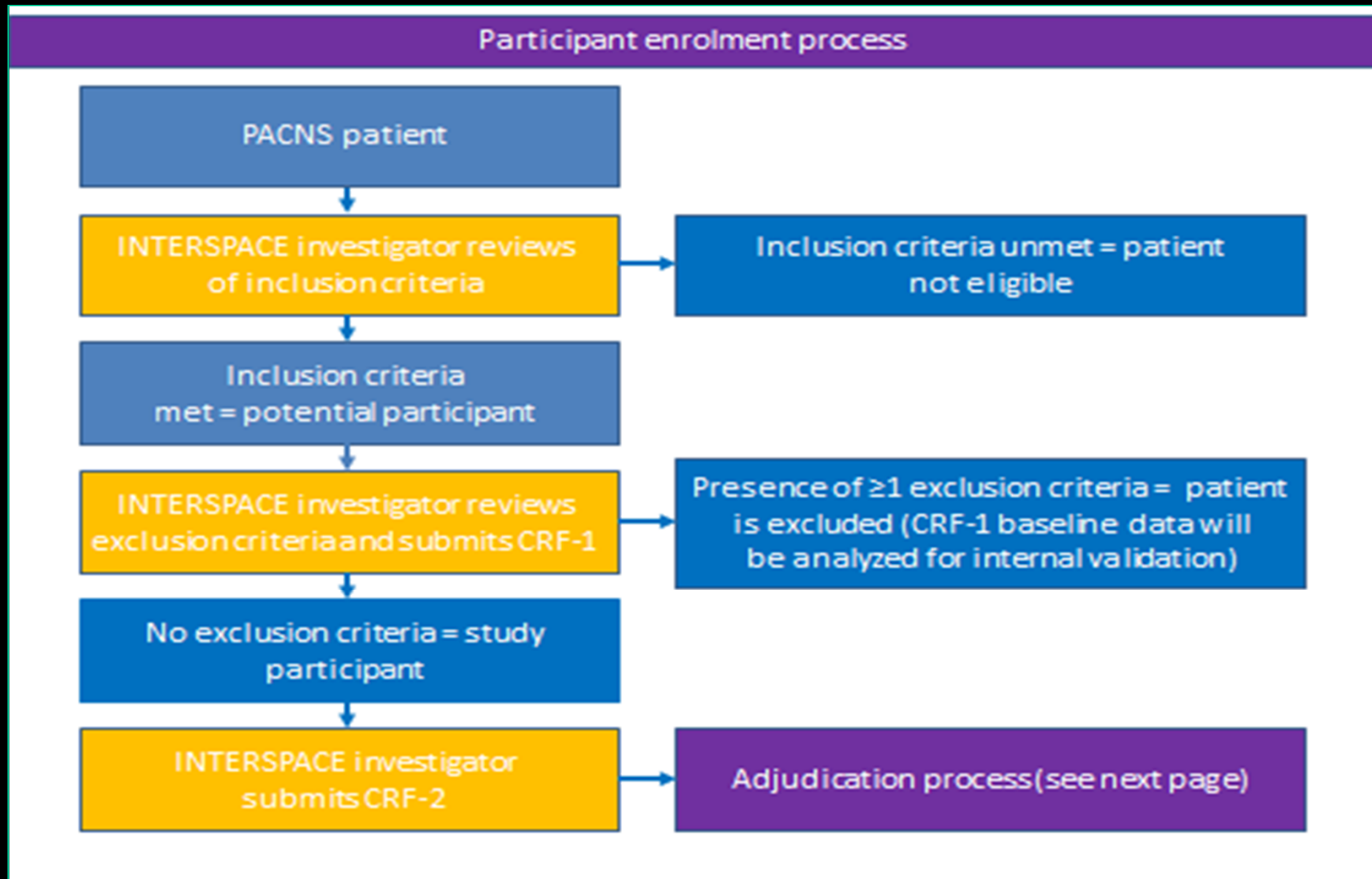
INTERSPACE: Data collection

Clinical data	
Demographics	Potential triggering factors
Lifestyle	Clinical manifestations
Past medical history	Neurological scales (mRS, MoCA, NIHSS)
Investigation	
Blood tests	
CSF analysis	
Brain and spinal cord imaging (T1, T2, FLAIR, GRE, DWI, ADC and gado.); Vascular imaging from the aortic arch to the brain (catheter angio., CTA and MRA)	Centralized review by blind NRad at the CHUM, using standard criteria
Histopathology	Centralized review by blind NPatho. at the Mass. General Hospital, Boston, using standard criteria)

INTERSPACE: Data collection

| Treatment |
|---|
| Antithrombotics |
| Corticosteroids and cytotoxic agents |
| Other therapies |
| Outcome |
| Treatment failures |
| Recurrent PACNS |

INTERSPACE: Implementation

Predefined clinical visits:

- Baseline: ≤14 days following initiation of immunosuppressant drugs
- Follow-up at 3 months, 6 months, 12 months, and at the end of each additional year
- When neurological decline (recurrence or treatment failure) is diagnosed

Data transmission:

- e-CRF available at <u>www.youngstrokenetwork.org</u> → Web-based database in Helsinki, Finland
- Brain, spinal cord and vascular imaging: Selected images downloaded on e-CRF for adjudication and complete set of images recorded on a CD and sent at the CHUM for analysis
- CNS histopathology: Selected images downloaded on e-CRF for adjudication and glass slides sent at the MGH for analysis

INTERSPACE: Implementation
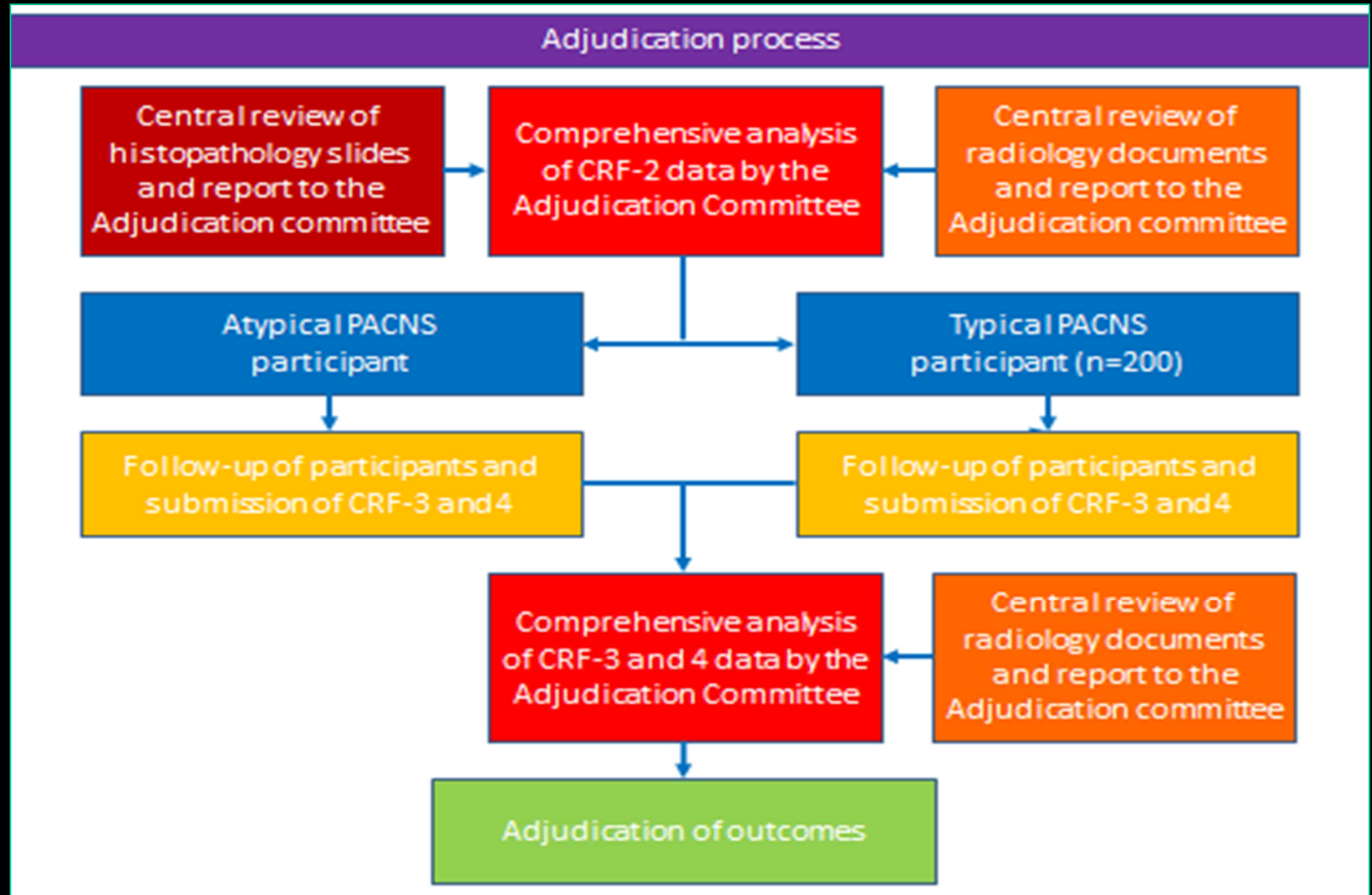
Adjudication process

INTERSPACE: Study projections

- 100 participating centres x 0.5 study subjects per year per centre x 4 years = 200 participants
- Follow-up≥1 year
- Study completion in 2018

INTERSPACE: the next steps

- Get REB approval and contracts signed from participating centres to start recruiting study subjects
- Increase the number of study sites with:
    - More sites from Asia, Africa, and Australia
    - More Rheumatology, other medical disciplines

CONCLUSION

- **INTERSPACE possible through the collaboration of a large number of study centres**
- **Minimal individual effort but a huge collective effort**
- **Many thanks to:**

Worldwide INTERSPACE investigators

Study subjects

Steering Committee: S Lanthier, LH Calabrese, JM Ferro

Database Committee (Helsinki, Finland): J Putaala, D Strbian

Histopathology Committee (Boston, USA): Matthew Frosch

Radiology Committee (CHUM, Canada): J Raymond, F Guilbert, L Létourneau

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