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Research Evaluating Sports ConcUssion Events—Rapid Assessment of Concussion and Evidence for Return (RESCUE-RACER): a two-year longitudinal observational study of concussion in motorsport

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ABSTRACT

Introduction Concussion is a clinical diagnosis, based on self-reported patient symptoms supported by clinical assessments across many domains including postural control, ocular/vestibular dysfunction, and neurocognition. Concussion incidence may be rising in motorsport which, combined with unresolved challenges to accurate diagnosis and lack of guidance on the optimal return-to-race timeframe, creates a difficult environment for healthcare practitioners.

Methods and analysis Research Evaluating Sports ConcUssion Events—Rapid Assessment of Concussion and Evidence for Return (RESCUE-RACER) evaluates motorsports competitors at baseline (Competitor Assessment at Baseline; Ocular, Neuroscientific (CArBON) study) and post-injury (Concussion Assessment and Return to motorSport (CARS) study), including longitudinal data. CArBON collects pre-injury neuroscientific data; CARS repeats the CArBON battery sequentially during recovery for competitors involved in a potentially concussive event. As its primary outcome, RESCUE-RACER will develop the evidence base for an accurate trackside diagnostic tool. Baseline objective clinical scoring (Sport Concussion Assessment Tool—5th edition (SCAT5)) and neurocognitive data (Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)) will be assessed for specificity to motorsport and relationship to existing examinations. Changes to SCAT5 and ocular, vestibular, and reaction time function (Dx 100) will be estimated by the reliability change index as a practical tool for trackside diagnosis. Neuropsychological (Cambridge Neuropsychological Test Automated Battery (CANTAB)) assessments, brain MRI (7 Tesla) and salivary biomarkers will be compared with the new tool to establish utility in diagnosing and monitoring concussive injuries.

Ethics and dissemination Ethical approval was received from East of England-Cambridge Central Research Ethics Committee (18/EE/0141). Participants will be notified of study outcomes via publications (to administrators) and summary reports (funder communications). Ideally, all publications will be open access.

Trial registration number February 2019 nationally (Central Portfolio Management System 38259) and internationally (ClinicalTrials.gov NCT03844282).

INTRODUCTION

Concussion is defined by the Concussion In Sport Group as: 'a traumatic brain injury induced by biomechanical forces'[1] and is diagnosed clinically according to a constellation of symptoms including alterations of mental state and consciousness.[2] The natural history is believed to be benign, but there is significant individual heterogeneity in its severity and rate of recovery, with longer recovery periods in certain demographics, such as adolescents.[3]

Amidst rising concern about concussion in contact sports,[4–7] there is scarce evidence in the scientific literature on the incidence, severity, and recovery of head injuries specifically in motorsport.[8] What little there is suggests that even though there has been significant investment in safety, drivers continue to experience a greater risk of concussion compared with other high-risk sports.[9] Furthermore, a recent survey in the international journal of motorsport medicine, *AUTO+Medical*, found that 70% of competitors: 'did not feel completely normal' when they attempted to return-to-race following concussion.[10] This landscape in the motorsport environment specifically—a relatively high concussion incidence combined with competitors returning before they have fully recovered—may leave competitors in control of a high-speed vehicle that poses an ongoing threat to the individual, other participants, and the public. Accurate identification of concussion and a

return-to-race decision supported by scientific evidence is therefore of vital importance in reducing the potential morbidity and mortality associated with concussion in motorsport.

Despite the importance of brain injury in motorsport, there exists only a small body of formal motorsport guidance for medical practitioners—resources which are often inconsistent and lack a scientific basis. The current mainstay of concussion assessment is a single clinical review reliant on self-reported patient symptoms, which are known to exhibit significant individual heterogeneity and to be variable in intensity over time. In areas of motorsport supported by a regular medical team, various assessment tools are used to assist with the return-to-race decision. Commonly, these tools are truncated versions of extended neurocognitive assessments which are most often used in the outpatient clinic, such as the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT[11]). ImPACT can provide objective data to interrogate specific deficits in memory, attention and fine motor skills, but can take up to 45 min to complete. A baseline assessment is advised, so that post-injury outputs can be directly compared with an individual's previous results. Although ImPACT has been used at varying levels of motorsport competition worldwide since the early 2000's, to date there has been no formal validation of its use for four-wheeled motorsport competitors specifically,[9] with only a single published study in motocross which does not include post-injury data.[12] In motorsport therefore, as in other high-risk sports, there is a growing need for an objective, rapid and accurate diagnostic tool for concussion, validated with sport-specific data.

Outside of current clinical practice in motorsport, there is an enlarging literature exploring the use of neuropsychological assessments applied to mild traumatic brain injury (mTBI) and concussion, with a recent focus on sports-related injuries. These assessments have become commonplace in the wider multidisciplinary clinical assessment of concussion in the outpatient setting and include examination of attention, working and long-term memory, social cognition, and awareness.[13] Recently, the detection of more subtle perturbations to neuropsychological function have been increased with the use of computerised testing platforms. However, the majority of these assessments are conducted within the acute post-injury period (largely 7–10 days after injury) and there remains some controversy regarding their timing and the lack of a proven relationship between other objective measures of concussive injury.[14] As a result, these instruments continue to have low positive predictive value and their sensitivity is variable, even when combined with neurocognitive testing.[15–19] Promisingly however, recent research has shown that the utility of these neuropsychological assessments can be augmented by exploration of executive function,[20] combined with test platforms designed for high-functioning participants, such as the Cambridge Neuropsychological Test Automated Battery (CANTAB; www.camcog.com). In addition, formal neuropsychological re-evaluation throughout the recovery period has demonstrated potential to assist with rehabilitation from concussive injuries.[21]

From the comprehensive assessment batteries utilised in clinic during the recovery period, 'sideline' screening tests distill the most pertinent features to support clinical decision-making on whether competitors are fit to resume participation acutely. These sideline concussion assessments offer a shorter alternative to outpatient clinic-based tools but remain relatively time consuming and can require specialist training. In addition, there is significant reliance on self-reported patient symptoms—a factor which is complicated by acknowledged under-reporting of concussion in motorsport specifically, a situation common in other sports.[22–24] Despite these potential difficulties, there are numerous tools available for rapid assessment. The Sport Concussion Assessment Tool (SCAT), now in its fifth version, is freely available for clinical use in both adult[25] and paediatric populations[26] and has recently been added to motorsport concussion management protocols in the UK (personal communication: Dr Paul Trafford, 2018). This development is encouraging, but as with the return-to-race tools described above, to date there has been no sport-specific validation of the SCAT5 relevant to motorsport, and thus its diagnostic utility in this setting remains formally unexplored.

An alternative but potentially rapid method of concussion assessment is analysis of brain injury biomarkers. Studies investigating biomarker levels in cerebrospinal fluid and blood have demonstrated validity in mTBI and concussion (Refs. 27 28 and 29–33, respectively), but their sampling is invasive and therefore impractical in the sporting environment. However, the recent discovery of the glymphatic system,[34] a waste clearance network for the central nervous system (CNS), provides a theoretical basis for the appearance of brain injury markers in a far more accessible body fluid—saliva. Indeed, there is a growing body of literature exploring the direct correlation between traditional protein biomarkers of brain injury and saliva[35]; however, a more promising avenue may be analysis of microRNA (miRNA). MiRNAs are noncoding molecules essential for transcriptional regulation and are detectable in a variety of body fluids, are stable in a variety of pH and are resistant to degradation by enzymes.[36] Studies have demonstrated potential for both diagnostic and prognostic use of their measurement in saliva for sports-related concussion in adolescent and adult populations, with recent work finding levels persisting for some weeks after the concussive event.[37]

In the absence of trackside testing facilities for biomarkers in the short term, attention has shifted to alternative methods of obtaining objective concussion assessment data. Historically, rapid clinical concussion assessments have relied on examination of the nervous system, based on the knowledge that neurosensory and balance-related effects are prevalent sequelae of brain injury.[38] By extension, an accurate concussion diagnosis

may theoretically be obtained by examination of optokinetic and vestibular reflexes, a method successful in discriminating concussed from control subjects with 89% sensitivity and 95% specificity using a static neurootologic test centre.[39] Technological advances mean that this signature of concussion can be captured in less than 10 minutes using a portable head-mounted display and eye-tracking system (certified as a Nonsignificant Risk Device by the Food and Drug Administration, and approved for clinical use—Regulation Number: 21 CFR 882.1460). The Neurolign Dx 100 device captures objective data relevant to ocular, vestibular, and reaction time (OVRT) function. It has been applied informally to motorsport populations since 2017, with a small North American dataset showing promise for the identification of concussion,[40] supported by a civilian cohort demonstrating improvement in OVRT assessment measures throughout the acute recovery period.[41] However, further motorsport-specific investigation is required to confirm the utility of Dx100 in the identification of concussion in this environment, in addition to its ability to monitor recovery acutely and therefore to assist with the return-to-race decision.

Despite encouraging advances in concussion assessment modalities and technologies, there remains uncertainty regarding the underlying neuroscientific basis of this type of brain injury. Many scientists and clinicians believe that the clinical picture is underpinned by cell membrane disturbance with impairment in neurotransmitter signalling within the CNS, but without permanent cellular injury.[42] There is potential to explore these disturbances with various forms of neuroimaging—a field which includes a wide range of technologies and data processing techniques capable of fundamentally changing our view of brain function in health, and after injury. MRI at 3 Tesla (T) can depict a wide range of phenomenon in the brain including structural changes, oedema, and haemorrhage, achieving resolutions of approximately 1 mm. More advanced MRI systems with static higher field strengths, such as 7 T, can reduce these resolutions to as low as 100 µm. In addition, it is possible to observe the blood oxygenation level dependent (BOLD) signal from the brain which varies in response to neuronal activity—the physical basis of functional MRI (fMRI). Using fMRI, the organising principles of brain function are now considered to be communications between regions rather than solely activity within the regions.[43] However, little is known about how the instruments described above as used in sports concussion assessment relate to the structural and functional neurobiological changes that may occur in the brain as a result of concussion.[44] Also untested is how neuroimaging might assist in the prediction of the time course for recovery after injury, and thus assist with the return-to-race decision in motorsport specifically.

The return-to-race decision is one of the most contentious issues in modern motorsport medicine, yet there is a paucity of scientific evidence available to clinicians. There are no formal studies exploring the decision in motorsport specifically; however, a small extant literature from road use suggests that both task and driving performance are reduced in the short-to-medium term following concussion.[45 46] Subsequent work advises that patients with concussion should not drive on the road for at least 24 hours after injury,[47] although this period of avoidance is suggested without strong evidence and later timelines are not explored. More broadly, current return to road driving guidance produced for medical professionals in the UK is provided by the Driver and Vehicle Licensing Agency (DVLA); however, concussion is not specifically addressed in the most recent document.[48] As regards to UK governance of motorsport activity, the national sporting body Motorsport UK published their first Concussion Guidelines in early 2016 which advised removing drivers from competitive racing activity for 14–21 days following a diagnosis of concussion.[49] This approach is mirrored by limited international guidance[50]; however, there are no published guidelines from the worldwide governing body for four-wheeled motorsport, the Federation Internationale de l'Automobile (FIA).

In summary, sports-related concussion represents a growing public health issue worldwide that is reflected in motorsport. The naturally highly engineered, highly monitored environment of this sport specifically provides a unique opportunity to interrogate the causative forces of concussion and its neuroscientific effects over time. Research Evaluating Sports ConcUssion Events—Rapid Assessment of Concussion and Evidence for Return (RESCUE-RACER) seeks to address the issues of diagnosis and return to race. It is composed of two studies evaluating motorsport competitors at baseline (CArBON) and post-injury (CARS), acquiring longitudinal data from the same participants where possible. Its primary objective is to contribute to the validation of promising rapid and objective diagnostic tools for concussion, providing data to assist clinicians with the safe removal of injured athletes from sports participation. It is also designed to establish the timeline to recovery after concussion associated with motorsport, creating an evidence base for the return-to-race decision. The potential lessons learnt from this programme may be applicable to the field of general sports concussion, in addition to the assessment and management of similar brain injuries sustained on the road.

METHODS AND ANALYSIS

The RESCUE-RACER programme is composed of two, mixed cross-sectional and longitudinal, observational, non-interventional studies of motorsport competitors aged at least 16 years. In the baseline study, Competitor Assessment at Baseline; Ocular, Neuroscientific (CArBON), healthy motorsport competitors will be recruited pre-injury to undertake clinical, neuropsychological, neurocognitive, biomarker, and OVRT assessments, in addition to brain MRI, as normative distributions for the post-injury study. CArBON will

create a sample-specific neuroscientific characterisation and act as a baseline for post-concussion follow-up. The post-injury study, Concussion Assessment and Return to motorSport (CARS), will recruit motorsport competitors exposed to a potentially concussive event, or diagnosed with concussion, during motorsport activity. The battery of assessments used in CArBON will be reapplied to follow CARS participants in the recovery phase of their injury. CARS participants need not have been previously enrolled into CArBON, although CArBON participants who are subsequently diagnosed with concussion can provide longitudinal data in CARS.

The overall objective of RESCUE-RACER is to establish the natural history of clinical symptoms and signs, neurocognitive, neuropsychological, and OVRT function and brain injury biomarker levels following concussion sustained in motorsport activity. MRI data will characterise the concussive injuries as a standard against which clinic assessments can be validated for sensitivity and specificity. The primary objective is to develop a trackside diagnostic tool for concussion comparing the utility of SCAT5 against assessment of OVRT function, quantifying severity immediately following injury and through recuperation during the acute recovery period. These data will form an evidence base for medical motorsport decision-making trackside, in addition to outpatient clinic management of potentially concussed competitors and completion of the return-to-race decision.

The RESCUE-RACER programme is being conducted over 2 years and aims to recruit n=50 participants into CArBON and n=70 participants into CARS. Participants may be enrolled in both studies. Written informed consent is obtained from adult participants, or from both the participant and parent/legal guardian for participants aged 16–18 years, in line with usual motorsport policy. Non-identifiable study data will be collected and managed using Research Electronic Data Capture tools hosted at University of Cambridge.[51 52]

Baseline study: CArBON

Inclusion and exclusion criteria for CArBON are outlined in table 1.

Sample selection: CArBON

Participants enrolled in the CArBON study are identified either by the Race Medical Director of the TOCA series (Touring Car Association; a UK-based motorsports event package registered as a Participant Identification Centre, PIC), or by the Team Principle of Aston Martin Racing (AMR, also registered as a PIC). The TOCA package consists of a number of semi-professional and professional competitive racing championships or series: three adult (British Touring Car Championship, Porsche Carrera Cup Great Britain, Michelin Ginetta GT4 Supercup); one mixed age group (Renault UK Clio Cup (replaced with the Mini Challenge in 2020), for drivers aged 17 years and over) and two adolescent (Simpson Race Products Ginetta Junior Championships, British Formula 4 Championship, for drivers aged 14 and above). Recruitment presentations are delivered by the Study Coordinator at TOCA events and AMR training days to potential participants, open to team managers, officials, race team staff, and competitors' relatives. Potential participants can provide their contact details at these events or use the study website (www.rescueracer.org) to contact the Study Team directly.

Assessments: CArBON

Assessments are made at one appointment which may take place across more than one session, at the participant's convenience. Full details of the assessments and their outcomes are in table 2. Demographic data include a minimum of age, sex, handedness, years of education, and years of motorsport experience. Participants complete a standard 10 minute paper-based sideline clinical assessment tool, the SCAT5[25] and the ImPACT[11]—a computerised neurocognitive test lasting for up to 45 minutes. These tests are part of the usual baseline or pre-season concussion assessment in motorsport. Assessment of OVRT function is completed with a 3D head-mounted display (Neurolign Dx100, previously known as I-Portal Portable Assessment System Nystagmograph, or I-PAS) which includes a combination of ocular, vestibular, auditory, and reaction time tests. An MRI scan is acquired at the Wolfson Brain Imaging Centre, University of Cambridge on a Siemens Magnetom 7T Terra scanner or the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 3 T, where 7 T is contraindicated. The scan protocol includes:

- T1-weighted MP2RAGE[53] scan, to depict brain anatomy with scan parameters: repetition time

Table 1 Baseline study (carbon) eligibility criteria

Study name	Inclusion criteria	Exclusion criteria
Baseline study (CArBON)	Competitive motorsport participants. Mental capacity to consent to study participation.	Age <16 years. Ongoing injuries so severe as to preclude study enrolment. Recent (within the last 4 months) or current involvement in a research study involving administration of trial medication. For MRI only: metal implants or exposure to metal foreign objects (such as welding), claustrophobia. Prior severe or moderate traumatic brain injury, diagnosis of mild traumatic brain injury or concussion within the last 6 months, symptoms of head injury at time of enrolment.

Table 2 Research Evaluating Sports ConcUssion Events—Rapid Assessment of Concussion and Evidence for Return assessments and their outputs

Assessment	Summary of data collected
Demographic assessment	Data collected within the clinical review: ► Participant demographics and medical history Name, address, date of birth, National Health Service number with MRN (local hospital identifier—where available), mobile number, up to two next of kin details (name, relationship, contact number), postal address, email address, general practitioner name and address, local hospital, medical and surgical history, current medications, allergies, family history, previous concussion assessments (type, number, date), time and date of last caffeine intake, the time from which the participant is advised to consume water only, if female—date of last menstrual period ► Motorsport history Current level of competition, highest level of motorsport, years at current level, total number of years in motorsport competition of any type, current competition car and class, use of: helmet, head and neck support or hybrid device; type of seat ► Concussion history Number of previous concussions and for each: date, setting, presence of loss of consciousness (LOC) and duration, confusion, retro/antero-grade amnesia (presence and duration), medical review, imaging, concussion assessment, time away from sport, referring hospital, length of admission, contact for medical information; estimated number of head injuries not formally diagnosed as concussion From ImPACT: ► Participant demographics and educational history Native country, native language, second language, completed years of education, previous completion of: speech therapy or special education classes, repetition of one or more school years, diagnosis of a learning disability, problems with attention deficit disorder (ADD) or hyperactivity ► Sporting history Current sport, level of participation, primary competitive event, years at this level ► Concussion history Number of concussions and for each presence of LOC, confusion, retrograde or anterograde amnesia; total number of sporting events missed due to concussion ► Potential confounding factors Treatment for: headaches, migraines, epilepsy or seizures, substance/alcohol abuse, psychiatric conditions (such as depression, anxiety); previous brain surgery or meningitis, diagnoses of: ADD or attention-deficit hyperactivity disorder (ADHD), dyslexia, autism; strenuous exercise in the last 3 hours, hours of sleep the night prior to testing, current medications. From CANTAB: age at assessment, handedness From MRI: current weight (kg) and height (cm), previous operations, presence of metal implants, previous brain injury or LOC
Sport Concussion Assessment Tool 5	► Symptoms—number (range 0–22) and severity (rated as 0–6), summed to form a symptom severity score (range 0–132), with higher scores indicating worse symptoms ► Orientation score (out of 5) ► Immediate memory score (out of 30) ► Concentration score (out of 5) ► Neurological examination (normal/abnormal) ► Number of balance errors (out of 30) ► Delayed recall score (out of 10)
Immediate Post-concussion Assessment and Cognitive Testing (ImPACT)	Demographics—see 'Demographic assessment' Composite and raw scores assessing: ► Attention (including processing) ► Memory (verbal and visual recognition (%); visual working) ► Visual motor speed ► Impulse control (response inhibition) ► Delayed memory (delayed repetition of verbal and visual memory tasks, %)
Neurolign Dx100 (Dx100)	► Ocular tests—saccades (vertical, horizontal, predictive, self-paced, memory-guided and anti-), smooth pursuit, optokinetic reflex, vergence, light reflex ► Vestibular tests—subjective visual vertical ► Reaction time assessments—auditory, visual

Continued

Table 2 Continued

Assessment	Summary of data collected
Cambridge Neuropsychological Test Automated Battery (CANTAB)	The CANTAB study protocol includes a variety of assessments across attention (processing and psychomotor speed), memory (visual episodic), executive function and decision-making (working memory and strategy; planning). Example tasks and their key outcome measures include: ► Spatial working memory (error, strategy) ► Reaction time (error scores, reaction, and movement times) ► Paired associates learning (error, number of trials to correctly locate patterns, stages completed) ► Multi-tasking test (performance during intermixed vs consistent rules and in/congruent information)
Saliva sample for biomarker analysis	To include, where possible, levels of: ► Neuronal injury such as neurofilament light chain (NFL) ► Glial injury such as S100B (a calcium-binding peptide) ► Epigenetic effects as measured by micro RNA levels (miRNA) ► Neurofibrillary degeneration as measured by tau
MRI of the brain	► High-resolution T1-weighted structural imaging ► Susceptibility-weighted imaging ► Diffusion-weighted imaging ► Resting-state functional MRI

(TR)=4300 ms; echo time (TE)=1.99 ms; flip angle (FA) = 5° and 6°; voxel size: 0.75×0.75 × 0.75 mm^3; a T2-weighted scan acquired with parameters: TR=8000 ms; TE=68 ms; FA = 130° voxel size=0.2×0.2×3mm^3 and a fluid-attenuated inversion recovery acquisition: inversion time (TI)=2400 ms; TR=9000 ms; TE=467 ms; voxel size: 1.0×1.0 × 1.0 mm^3.

- Susceptibility weighted imaging, sensitive to susceptibility variations caused by venous blood and haemorrhages, is acquired with multi-echo scan parameters: TR=30 ms; TE1=4.57 ms, TE2=7.92 ms, TE3=11.27 ms, TE4=14.62 ms, TE5=17.97 ms, TE6=21.32 ms; FA = 15°; voxel size=0.6 × 0.6 × 0.7 mm^3.
- Diffusion weighted imaging, sensitive to motion of water, is acquired with scan parameters: TR=7240 m; TE1=56 ms TE2=84 ms; b-values=0 s/mm^2 and 1000 s/mm^2; 20 directions; voxel size=1.4 × 1.4 × 1.4 mm^3.
- fMRI, sensitive to BOLD contrast, is acquired with TR=1713 ms; TE=20 ms; FA = 60°; Voxel size=1.4 × 1.4 × 1.4 mm^3; 700 volumes.

Neuropsychological assessments are completed using the CANTAB touchscreen battery (www.camcog.com), using a study-specific protocol which includes the following tasks: spatial working memory (assessing working memory and strategy), reaction time (assessing processing and psychomotor speed), paired associates learning and the multi-tasking test. After an oral rinse with tap water participants provide a saliva sample in sterile containers.

Where possible, all CArBON assessments will take place on the Addenbrooke's Hospital site, to provide a comparable testing environment to the post-injury assessments for CARS. To explore the effects of collecting data in a motorsport environment (which will be necessary for data collected in the immediate post-injury period as part of the CARS study), a subset of CArBON participants will complete portable assessments from the baseline battery at venues for motorsport competition.

Post-injury study: CARS

Inclusion criteria: CARS

Exposure to a potentially concussive event during motorsport activity or a diagnosis of concussion made by an experienced clinician less than 3 weeks prior to referral. Aside from history of previous brain injury, all other inclusion and exclusion criteria are identical to those for CArBON (table 1). To increase consistency in the diagnosis of concussion, referring clinicians will be encouraged to use the Motorsport UK Concussion Guidelines[49] which will be presented, demonstrated, and discussed during educational events for motorsport medicine practitioners delivered prior to and during recruitment to CARS. Where available, the factors used by clinicians to make the diagnosis will also be recorded in the study database.

Sample selection: CARS

Most potential CARS participants are identified by the Race Medical Director for TOCA following involvement in a potentially concussive event during motorsport activity supported by TOCA. The Race Medical Director will make the initial approach to potential participants, where practicable, after serious injury is excluded by an independent medical practitioner. CARS participants may also be referred directly to the Chief Investigator.

Assessments: CARS

Portable study assessments (which include SCAT5, OVRT assessment, ImPACT, CANTAB, and saliva collection) can, where appropriate, be completed at race circuits immediately following the concussive injury and after completion of informed consent. Participants then attend the Sports Concussion Clinic at Addenbrooke's Hospital, Cambridge and complete weekly assessments at 1, 2, and 3 weeks post-injury. This schedule will be independent of recovery from concussion, so that serial assessment data from CARS may be used as controls.

Should symptoms persist beyond this time, the participant is offered an additional two assessments at monthly intervals. All data collection methods mirror that of CArBON, including the MRI scanning protocols. In addition, participants can choose to provide consent for the Study Team to access one or more of: their motorsport records (medical notes, previous concussion assessments, and accident data) and medical notes (including contact with their general practitioner). Should this consent be provided, the Study Team are able to include additional data from the incident which may include: car telemetry, accident data recorder (ADR) outputs, in-ear accelerometer (IEA) data, and incident footage (either in-car or from the circuit).

Sample size calculations

The proposed sample sizes for CArBON (n=50 competitors assessed at baseline) and CARS (n=70 competitors involved in a potentially concussive event) are thought to be both feasible and sufficient to sample the wide heterogeneity of concussion in motorsport and to result in a clinically significant primary outcome. Where possible, repeated measures data from CArBON for those individuals later invited to participate in CARS will be longitudinal and form a qualitative narrative of the competitor's neuroscientific profile as it evolves after involvement in a potentially concussive event.

Data analysis plan

The overall context of the study is to map the natural history of concussive symptoms and signs in motorsport immediately post-injury and throughout the recovery period. First, we will cross validate existing diagnostic tools using datasets collected in CArBON, then develop a new trackside diagnostic tool against which additional technologies can be validated.

Validation of existing diagnostic tests

Subject to appropriate ethical approvals, distributions of SCAT5 and ImPACT scores collected in CArBON (from non-concussed competitors) will be compared with samples collected from other sports participants (potential datasets include[54 55] and,[15 56–60] respectively) by comparison of central tendencies and qq-plotting to establish whether there is a need for sport-specific samples. The shared variance between SCAT5 and ImPACT total scores will be tested by correlation and an exploratory factor analysis will be undertaken across item scores. These tests will be used to characterise current concussion evaluation in motorsport following injury and during recovery.

Designing a trackside diagnostic tool

Practicalities limit the types of test that can be administered trackside or at other venues where motorsport incidents occur. Thus, a priori, SCAT5 and OVRT assessments are the key measurements, together with history of concussive injuries, that will first be developed as a new diagnostic tool. This new tool is required to be both rapid and compact and therefore in the first instance dimension reduction will select components that explain at least 80% of the variance from non-concussed (CArBON) data collected for each instrument. Test–retest reliabilities for these components will be estimated from longitudinal data, where available. CARS data from participants with clinically confirmed concussion will represent the true post-injury dataset. Individuals who have been exposed to a potentially concussive event, but who are not diagnosed with concussion will form a control cohort for these post-injury assessments.

The reliability change index (RCI[61 62]) will be calculated for each component for each individual subsequent to a potentially concussive brain injury and for whom longitudinal data are available from CARS. Statistical significance of the RCI is 1.96 ($p<0.05$). Clinical significance will be determined according to criteria outlined by Jacobson and Truax[62]: that the pre-to-post injury difference score (ie, CArBON to CARS) is greater than the RCI and that the recovered post-injury scores (CARS participants who have clinically recovered) fall within the range of normative values from CArBON. The clinical relevance of the chosen components will be verified by between-subject correlations of observed changes. These calculations will be made immediately post-injury and in the follow-up period.

As sample size and experience accumulates, guidelines for clinical use of the new test for diagnosis and return-to-race decisions will be updated and the empirical relationship between the number of components with statistical and clinical significance and their associated magnitudes of RCI to patient reports of symptom severity and unmeasured comorbidities.

Validation of new modalities to measure concussion

Exploratory investigations will take place to assess the relationships between MRI, CANTAB and saliva-derived biomarker levels to the SCAT5 and ImPACT non-concussed measures acquired in CArBON.

MRI

From T1-weighted structural MRI, voxelwise grey matter volume are estimated with FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM). Cortical thickness is estimated using the Freesurfer package (https://surfer.nmr.mgh.harvard.edu).

Functional MRI

Functional connectivity will be estimated between all brain regions, defined using a standard atlas, as correlations of BOLD-sensitive fMRI signal acquired during rest in a graphical representation of nodes (regions) connected by weighted connections (edges): the functional connectome.[43] The connectome can then be characterised by graph theoretical parameters of local and global efficiency in the whole-brain connectome as well as seven large-scale networks related to specific cognitive domains.[63]

Susceptibility weighted imaging

Following identification and removal of non-brain tissues from the image, the STI suite (10.1002/nbm.3056) will be used to undertake quantitative susceptibility mapping. This process computes tissue magnetic susceptibilities by first unwrapping the measured phase images and then removing contributions due to background susceptibilities.

Cambridge Neuropsychological Test Automated Battery

Details of the tasks and outcome variables for neuropsychological assessment are given in table 2. Post-injury neuropsychological assessment data from CARS will be compared with the motorsport-specific baseline (non-concussed) dataset collected during the CArBON study. Subject to appropriate ethical approvals, participants aged over 18 years may be compared with CANTAB's own normative database (including up to 3000 adult healthy volunteers ideally matched for both gender and age), or from other relevant publications.[64] Longitudinal analysis will be performed for participants enrolled in both CArBON and CARS, and for CARS participants with more than one study visit, in order to investigate acute and long-term alterations in neuropsychological function using a programme such as IBM SPSS Statistics or similar. In the first instance, this analysis will focus on key outcome measures identified in the CANTAB Connect Research Overview Document (see table 2). Thereafter, we will explore domains relevant specifically to the performance of motorsport competitors within each test variant (such as reaction and movement time responses).

Salivary biomarkers

Saliva samples will be analysed either in Cambridge or at collaborating UK institutions in order to explore a variety of potential biological mechanisms for concussion including: neuronal injury (measured by levels of neurofilament light chain, NFL), glial injury (for which a proxy measurement may be levels of S100B, a calcium-binding peptide), control of gene expression (as measured by levels of a panel of micro RNA, miRNA) and finally neurofibrillary degeneration (as measured by levels of tau). Where appropriate, concentrations of these example potential biomarkers will be expressed as median and 25th–75th percentiles. Statistically significant differences will be identified by standard group comparison statistics (ie, the t-test for normally and the Mann-Whitney U two-sided test for non-normally distributed data). For comparison between proportions, Fisher's exact test will be used. Statistical significance for all analyses will be $p<0.05$. The objective of these analyses is assessment of the strength of association between the miRNA panel or other brain injury biomarkers in concussed participants at the time of injury (CARS trackside) compared with competitors without concussion (CArBON), evaluated with Pearson correlations. Where possible non-concussed CARS participants will be compared with concussed CARS participants to explore the effects of an incident without brain injury. Pearson correlations will also be used to interrogate the saliva sample analysis to explore the kinetics of these biomarkers in the post-injury cohort (CARS) serially throughout recovery (at weeks 1–3) compared with competitors without concussion (CArBON) and competitors participating in motorsport but not involved in an incident (CArBON). Where data are available, similar statistical methods will be used to correlate salivary biomarker levels with demographic information, including the severity of concussion, as well as the type and duration of symptoms, and time taken to return to participation in motorsport.

Finally, correlations between post-injury SCAT5 and ImPACT scores (or 'pre-injury and post-injury differences') and each output variable in each domain described above (in addition to the corresponding principal components) will be estimated and ranked according to effect size.

Patient and public involvement

Prior to drafting the study protocol, an informal investigation into the acceptability and design of RESCUE-RACER and the plan for result dissemination was conducted with TOCA competitors (2016 and 2017 seasons). Clinical encounters were used as a platform for discussion (specifically attendance for baseline neurocognitive testing with the Study Coordinator). Approximately, 80 drivers completed neurocognitive testing in 2016, with a large proportion successfully engaged in a short semi-structured discussion about RESCUE-RACER. In 2017, discussions outside of clinical encounters were conducted with a variety of motorsport personnel including team managers, championship administrators, Race Stewards, and Scrutineers, as well as members of the medical and rescue teams, in addition to relatives of drivers and guardians/legal representatives of adolescent competitors. Review of the priorities, experiences and preferences from each of these stakeholder groups had a significant positive influence on the final protocol, allowing the recruitment strategy, assessments, their schedule, and the dissemination plan to be tailored to this specialised population. For example, tasks within the CANTAB and OVRT protocols were reordered to minimise participants' frustration and reduce anxiety over time pressure, the latter often being a significant barrier to engagement with non-essential tasks within motorsport.

DISCUSSION

Although a common injury in sport, concussion remains both enigmatic and heterogenous in its mechanism, individual symptom profile, and subsequent resolution. Recent investigations are beginning to uncover the acute and chronic sequelae of concussive brain injuries in sports specifically, with directly observable consequences to the way sports are medically managed and even played already evident worldwide. Within this landscape, motorsport offers a unique environment to study mild traumatic brain injuries, since at many levels of

the sport competitors are monitored prior to and even during the competitive season. When incidents occur, they are recorded in remarkable detail utilising a wealth of data sources including circuit footage, in-car engineering data (commonly termed 'telemetry'), and, where supported, IEA systems. In addition, many competitors now routinely also record their own competition footage with increasingly sophisticated in-car camera systems. Moreover, comprehensive medical assessment and treatment is the first response to any incident in motorsport, with on-scene arrival times orders of magnitude quicker than usual responses to similar incidents on the road. This rapid-response, data-rich environment therefore provides a unique opportunity to correlate changes in clinical function to the causative forces associated with concussive brain injuries.

The potential and serious health, social, economic, and personal consequences of a concussive brain injury are universally acknowledged for the individual and society. Therefore, it is imperative in any sport that an accurate on-site diagnosis and assessment tool, in addition to a clear return-to-participation decision protocol, are supported by a credible clinical, neuroscientific, and psychological evidence base. This must be a priority across all sporting disciplines and motorsport is no exception. RESCUE-RACER addresses this unmet need for car racing in the first instance, but it is hoped that the lessons learnt will be applicable to other forms of motorsport, other sporting disciplines, and the roads alike. This novel research programme will collect high-quality clinical research data not only from the usual hospital environment, but also from an unusual prehospital setting. Collection of concussion assessment data from motorsport circuits specifically, acknowledged by the authors as a challenging and as yet unexplored environment, represents a real opportunity to bring academic clinical research into new real-world environments. The lessons learnt from the creation, support, and realisation of this research programme will be applicable to future research in similar environments relevant to clinicians working pitchside, trackside, and beyond.

In the first instance, the results of the RESCUE-RACER programme will be directly relevant to the diagnosis of concussion and return-to-race decisions in helmeted forms of two-wheeled motorsport including motorbike competition and motocross, where formal guidance is lacking. Beyond this, the results of this concussion in motorsport programme may be relevant to patients injured during road traffic collisions, especially road users travelling in motorised vehicles. Wider still, the dataset generated by RESCUE-RACER will also be relevant to the larger athletic community, publishing detailed baseline and post-injury data for the SCAT5. This freely available and rapid pitchside SCAT is currently used in almost all sporting disciplines; however, interpretation of its results is limited by a lack of publicly available data, especially with regards to thresholds for concussion identification. RESCUE-RACER will specifically address this unmet need. Outside of the sporting environment, the potential for rapid and accurate concussion assessment using technologies such as Dx100 will be relevant to the assessment of concussion of any cause, in any medical setting. In particular, the creation of a rapid diagnostic protocol by the RESCUE-RACER programme has the potential to significantly expedite assessment in busy secondary care environments, with special relevance to time-pressured emergency departments. Finally, novel application of the computerised neuropsychological battery CANTAB to a specific subset of patients with mTBI represents a potential opportunity to remotely monitor recovery and guide rehabilitation. If successful, this digital assessment tool will be particularly relevant to clinicians operating in the post-COVID19 era, where face-to-face assessments are not always logistically feasible.

Of course, development of a diagnostic and prognostic tool is not the end of this journey, but the beginning of an evolutionary process to improve its sensitivity and specificity in the light of new information. This study contributes to the start of that process, testing and ranking contemporary technologies in OVRT assessment, brain imaging, neuropsychology, and analysis of salivary markers relevant to brain injury, inflammation and potentially neurodegeneration. These approaches, and others, could be incorporated into future versions of the output diagnostic tool if practicalities permit but, in addition, they may also clarify the microscopic and macroscopic mechanisms that underlie the biological insult of a concussive injury and subsequently its sensory and behavioural sequelae.

While accurate diagnosis is key to subsequent clinical management of individual patients, the effectiveness of introducing new tools and protocols to the any sport requires long-term monitoring. Physical and neurocognitive evaluations are currently a regular and mandatory component of participation in UK and most international motorsport; however, this is known to vary according to level of competition, venue, and country. In the coming seasons, we will collaborate with national and international regulatory motorsport bodies to maintain records on changes in the number, severity and symptom profiles of concussive incidents experienced by motorsport competitors. Our overarching objectives are to improve the overall welfare of motorsport competitors in the near term as well as in the future, and to sustain this improvement in the decades to come.

ETHICS AND DISSEMINATION

Prior to initiation of any assessments and for all studies, written informed consent is obtained from adult participants, or from both the participant and parent/legal guardian for participants aged 16–18 years, in line with usual motorsport policy.

Participants will be notified of the programme outcomes via provision of relevant publications to the TOCA or AMR administrators and by inclusion of summary reports in Funder communications. Participants may specifically

request their individual results from the Chief Investigator, which may be provided after publication of the overall study results.

Where possible, all publications will be in open access journals. There is a plan to make the study protocol freely available. There is no plan to make the full study report, anonymised participant level dataset or statistical code for result generation publicly available; however, these data can be shared on reasonable request.

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Contributors Authorship will be determined in accordance with the guidance provided by the International Committee of Medical Journal Editors (available on request). PJH conceived of the study. All authors initiated the study design and participated in implementation. The motorsport adapted SCAT5 was drafted by PJH and NDD, with informal input from motorsport colleagues (specifically early edits of the Maddock's questions). The RESCUE-RACER CANTAB protocol was created by NDD. The RESCUE-RACER OVRT protocol (first on I-PAS, later for Dx100) was created by NDD, with input from Neurolign's Vice President of Technology Development (Alex Kiderman; AK). The RESCUE-RACER saliva collection protocol was drafted by NDD, with advice from colleagues at the University of Birmingham and use of text from the Dex-CSDH Trial sub-study protocol (available on request). The RESCUE-RACER 7 T MRI protocol was drafted by JS and NDD with significant input from WBIC radiologists and in-house physicists Chris Rogers (CR) and Catarina Rua (CRu). A similar 3 T protocol was created by CRu and JS, with input from NDD, CR and assistance by Debora Macedo (DM). RESCUE-RACER data capture tools on REDCap were created by NDD and DM, with input from Joe Fryer (JF). NDD and JS drafted the initial study protocol submission; all authors contributed to manuscript revisions. All authors read and approved the final manuscript, which was reviewed by the Funder (FIA), technology collaborator (Neurolign) and representatives of TOCA prior to submission.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval The RESCUE-RACER programme received ethical approval from the East of England - Cambridge Central Research Ethics Committee on 14/08/2018 (REC reference: 18/EE/0141). RESCUE-RACER is an observational study and does not require appointment of an independent Data Monitoring Committee or management by a Study Steering Group. The study protocol has been reviewed by the Scientific Advisory Committee of the FIA in an independent, expert, and proportionate peer review process (decision communicated on 15/02/2018). Any amendments to REC approval have been managed in line with national UK guidelines.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets are generated and/or analysed for this study protocol. However, the investigators are happy to receive requests from bona fide researchers for access to study data (subject to review by the RESCUE-RACER collaborators) and can provide support for future analyses.

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