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LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – multicentre, randomized cross-over clinical trial protocol

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41 **ABSTRACT**

42 **Introduction**

43 Attention deficit hyperactivity disorder (ADHD), which affects 5-10% of the general pediatric
44 population, was reported to be more common in children with T1D in whom it ADHD
45 exacerbates the clinical course of T1D. Proper pharmacological treatment of ADHD in such
46 patients may thus have a beneficial neurological and metabolic impact. To address this issue,
47 we designed a non-commercial 2nd phase clinical trial comparing the impact of different
48 pharmacological interventions for ADHD in children with T1D.

49 **Methods and analysis**

50 The study is a multicentre, randomized, open-label, cross-over clinical trial in children and
51 adolescents with ADHD and T1D. The Trial will be conducted in four reference pediatric
52 diabetes centres in Poland. Over 36 months, all eligible patients with both diagnoses of T1D
53 and ADHD (aged 8-16.5 years, T1D duration >1 year) will be offered participation in the Trial.
54 Patients will be enrolled in an online once-weekly parental training in behavior management
55 for ten weeks. Afterward, they will be randomized to pharmacotherapy groups:
56 methylphenidate (long-release capsule, doses 18-36-54mg) versus lisdexamphetamine (doses
57 30-50-70mg). Treatment will continue for 6 months before switching to alternative
58 medication. Throughout the Trial, the participants will be evaluated every three months by
59 their diabetologist and online psychological assessments. The primary endpoint (ADHD
60 symptom severity in the Conners 3.0 questionnaire) will be assessed by a blinded investigator.
61 Secondary endpoints will include HbA1c, CGM indices, and Quality of Life (PedsQL).

62 **Ethics and dissemination**

63 The trial is approved by the local Bioethical Committee and Polish administrative body
64 (RNN/142/22/KE, UR/DBL/D/263/2022). The Trial results will be used to improve ADHD
65 treatment in children with T1D. Treatment efficacy and the dual psychiatric and metabolic
66 benefits will be used to evaluate the economic feasibility of using LDX in patients with both
67 diseases. Additionally, the Trial will promote collaboration between mental health
68 professionals and diabetes teams.

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3 70 **Strengths and limitations of this study**
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5 71 **Strengths:**

- 6 72 • Multicentre trial on a vulnerable population and complex, unaddressed clinical issue of
7 73 neurodevelopmental and metabolic comorbidity.
8
9 74 • Blinded assessment of primary endpoint, use of structured and validated questionnaires
10 75 for diagnosis and assessment.
11
12 76 • Direct comparison of drugs via cross-over design with planned dose-optimization
13 77 protocol.

14
15 78 **Limitations:**

- 16 79 • Patients and physicians not blinded to the drug, possible expectation bias.
17
18 80 • A moderate risk of selection bias – exclusion of patients with more complex psychiatric
19 81 phenotypes. Caregivers and patients reluctant to stimulant medication drugs may be
20 82 unwilling to participate.
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24 84 **Keywords:**

25 85 Attention-deficit hyperactivity disorder, type 1 diabetes, methylphenidate,
26 86 lisdexamphetamine, clinical trial, HbA1c,
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87 Introduction

88 ADHD effect on type 1 diabetes treatment

89 Type 1 diabetes (T1D) is a common metabolic disease in childhood affecting over one million
90 young people worldwide, with an age-standardised incidence of 31/100,000 in Europe, and
91 16/100,000 in Poland (0-19 years, per 100,000 per year)^{1,2}.

92 Recent advantages in medical technology improved glycemic control and significantly
93 reduced rates of diabetes complications^{3,4}. However, state-of-art therapy of T1D is highly
94 demanding for the patient as it requires multiple actions throughout the day e.g. frequent
95 blood glucose monitoring, counting of carbohydrates intake, and adjustments of
96 administered insulin doses. To benefit from such intensive treatment, a child needs efficient
97 executive functioning and a high level of self-control – and those who lack those abilities
98 might face the gap between expected and achieved outcomes.

99 In particular, comorbid psychological and neurodevelopmental disorders, including attention-
100 deficit/hyperactivity disorder (ADHD), were shown to impair diabetes management⁵⁻⁸. ADHD
101 is a neurodevelopmental disorder affecting 5-10% children⁹. The problem of ADHD is
102 especially relevant due to the reported 35% (OR 1.35; 95% CI: 1.08–1.73) increased risk of
103 ADHD in patients with T1D compared to healthy peers¹⁰. A Swedish active screening of
104 children with T1D showed that among children with newly diagnosed ADHD, 77.8% had
105 inadequate metabolic control (mean HbA1c>8.6%) compared to 42.9% in the group of
106 children with treated ADHD¹¹. Association between ADHD and poor T1D control were
107 reported by German and Israeli studies^{12,13}. As a result of deteriorated metabolic control,
108 those patients experience an elevated risk of life-threatening episodes of severe
109 hypoglycemia or ketoacidosis, resulting in prolonged hospitalizations^{10,14,15} and long-term
110 complications, such as diabetic nephropathy⁵. In that perspective the need for evidence
111 regarding the effectiveness and safety of ADHD treatment in pediatric T1D emerges as a
112 pertinent clinical challenge.

113 Current ADHD treatments and their effects on type 1 diabetes

114 No randomized clinical trials (RCT) have been conducted regarding the effectiveness and
115 safety of ADHD treatment with coexisting T1D. Therefore, despite the tremendous impact
116 that both conditions have on patients' everyday life, current clinical guidelines on the
117 psychological management of T1D do not address the problem of ADHD¹⁶.

118 Many European therapeutic guidelines recommend environmental modifications or
119 psychosocial intervention as first-line treatment for children with ADHD¹⁷⁻¹⁹. Parent training
120 in behavior management (PT) is a psychosocial intervention aimed at improving caregiver's
121 understanding of ADHD symptoms and helping them acquire skills to deal with everyday
122 challenging behavior and support child development. Although PT improves parenting and
123 reduces conduct problems, meta-analyses found no effect of PT on core ADHD symptoms
124 when raters were blinded to the treatment allocations²⁰. If, despite PT, symptoms of ADHD
125 persist and cause significant impairment of daily functioning, pharmacotherapy is
126 recommended.

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3 127 Two psychostimulants with well documented effect and tolerability in ADHD are
4 128 methylphenidate (MPH) and lisdexamphetamine (LDX). Stimulants have higher effect sizes on
5 129 ADHD core symptom reduction than non-psychostimulating medications and their dosage is
6 130 easier to adjust^{21,22}. In Poland, long-acting MPH formulations are considered the first-line
7 131 pharmacotherapy for ADHD²³. LDX, contrary to MPH, is an inactive prodrug that requires
8 132 enzymatic conversion, resulting in an extended and more stable acting time (~13h). In most
9 133 international guidelines, LDX is advised first line treatment comparable to long-acting MPH,
10 134 or as a secondary drug after treatment failure with previous MPH medication attempts²². In
11 135 Poland LDX is neither reimbursed by the National Health Fund (NHF) nor commercially
12 136 available.

13 137 Limited retrospective data demonstrates that patients with ADHD and T1D treated with
14 138 stimulants show lower HbA1c ($8.1\pm 1.0\%$) compared to children that were diagnosed but not
15 139 treated pharmacologically ($8.5\pm 1.1\%$)²⁴. At the same time, others reported higher blood
16 140 pressure and no difference in metabolic control^{12,13}. However, generalization of those results
17 141 remains limited due to the low sample size, lack of evidence from RCTs, and no direct
18 142 comparisons between LDX and MPH. In conclusion, there is a lack of data on the safety and
19 143 effectiveness of ADHD medication in children with T1D regarding the effect on ADHD
20 144 symptoms, quality of life, and metabolic control.

21 145 **The aim of the Study**

22 146 The Trial aims to compare the safety and efficacy of ADHD treatment with LDX or MPH in
23 147 children and adolescents with ADHD and T1D in improving ADHD symptoms, T1D control, and
24 148 patient's quality of life.

25 149 **Methods and analysis**

26 150 **Study design and population**

27 151 LAMAIinDiab is a phase 2 randomized cross-over open clinical trial with blinded endpoint
28 152 assessment. The project is funded by the Medical Research Agency. This public agency
29 153 provides financing for non-commercial clinical trials in Poland through open calls. Upon
30 154 application for financing of the trial, the project consortium was established, and four
31 155 recruiting sites – that collectively provide care for ~25% of national pediatric population with
32 156 T1D^{25,26} – were declared within the grant application and remained unchanged thereafter.

33 157 **Patient and Public Involvement statement**

34 158 The project's idea was consulted with and supported by a national patient organization
35 159 (Polish Federation for Support of Children and Adolescents with Diabetes, "Diabetycy.eu"). As
36 160 a result, the organization entered consortium leading the project. Clinical trial's design and
37 161 protocol were thoroughly consulted with the organization, and its representative (MZ) was
38 162 included among the authors to acknowledge her input. Subsequently, the organization's
39 163 qualified representatives agreed to play the roles of independent investigators blinded to the
40 164 treatment allocation and perform ADHD symptom assessments for participating children.

41 165 **Inclusion and exclusion criteria**

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3 166 Principal inclusion criteria:
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- 5 167 • Age 8-16.5 years at trial entry;
6
7 168 • T1D diagnosed according to National and International Guidelines^{27,28} at least 12 months
8 169 before recruitment, treated with functional intensive insulin therapy,
9
10 170 • ADHD diagnosis according to 5th Edition Diagnostic and Statistical Manual of Mental
11 171 Disorders (DSM-5)²⁹ or International Statistical Classification of Diseases (ICD-10)³⁰ and
12 172 confirmed as consistent with DSM-5 by a psychiatrist;
13
14 173 • Polish citizenship and health insurance.

15 174 Principal exclusion criteria:
16

- 17 175 • Clinical partial remission of T1D (daily insulin dose < 0.3 j/kg and concomitant HbA1c
18 176 measurement ≤ 6.5% from the last 3 months) or severely unsatisfactory glycemic control
19 177 (mean HbA1c over the past year ≥ 12%, excluding HbA1c measurement at T1D diagnosis);
20
21 178 • Clinically apparent or previously-diagnosed cardiovascular disease: hemodynamically
22 179 significant heart defect, advanced vascular atherosclerosis, or documented hypertension
23 180 (at least stage 2);
24
25 181 • Diagnosed intellectual disability or other disability that prevents patient adherence to its
26 182 therapeutic regimen; history of other mental illness or disorder preventing participation
27 183 in the trial, e.g. bipolar disorder, schizophrenia, other psychotic disorders, history of
28 184 suicide attempts or present suicide intentions, psychoactive substances abuse;
29
30 185 • Contraindications to either studied drug. Language barrier making it impossible to conduct
31 186 a full psychological consultation in Polish, lack of permanent residence and national
32 187 insurance in Poland;
33
34 188 • Inability of the parents/legal guardians' to come to the Centre at the time specified by the
35 189 protocol, in particular – to pick up the study drugs at the dose adjustment stage (the need
36 190 to pick up 4-5 times over 6-8 weeks, each time within 2-3 days of receiving the
37 191 recommendations);
38
39 192 • Other reasons that, in the opinion of the attending physician, are more likely to result in
40 193 difficulties in maintaining the participant's participation in the trial or harm to the
41 194 participant's health in case of participation in the trial.

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44 195 **Setting**
45

46 196 The Trial will be conducted in 4 pediatric diabetology centres, and apply telemedical tools to
47 197 facilitate recruitment, improve compliance and reduce the burden on participants and their
48 198 families. The participating centres provide coordinated pediatric diabetology care for their
49 199 respective voivodeships (regions of Poland):

- 50
51
52 200 • Lodzkie voivodeship: Department of Pediatrics, Diabetology, Endocrinology and
53 201 Nephrology, Pediatric Centre of the Central Clinical Hospital of the Medical University of
54 202 Lodz;
55
56 203 • Silesian voivodeship: Department of Children's Diabetology, Medical University of Silesia,
57 204 Upper Silesian John Paul II Child Health Centre;

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3 205 • Pomeranian voivodeship: Department of Pediatrics, Diabetology, and Endocrinology of
4 206 the Medical University of Gdansk, University Clinical Centre in Gdansk;
5
6 207 • Opole voivodeship: Department of Pediatrics of the Institute of Medical Sciences of the
7 208 University of Opole (Department of Pediatrics and the Diabetology Clinic for Children of
8
9 209 the University Clinical Hospital in Opole).

10
11 210 Information about the centres was published on the project's website -
12 211 <https://lamaindiab.umed.pl/>. Pediatric diabetology centres included in the trial are public
13 212 care providers – the trial visits and procedures will be carried out as add-ons to routine visits
14 213 related to the management of diabetes. Pediatric healthcare in Poland is tax-financed by the
15 214 NHF and provides universal, free-of-charge care for all children registered in Poland and their
16 215 caregivers.

19 216 **Summary of trial procedures**

20 217 Patients with ADHD and T1D, meeting the clinical trial's inclusion criteria may enroll into the
21 218 Trial in the designated reference centres. First, their guardians will receive information about
22 219 the study from the centre's representative via phone, followed by complete Information and
23 220 Consent forms sent to agreed mail address. During the next routine outpatient consultation,
24 221 the guardians and children will thoroughly discuss the information provided with an
25 222 investigator. After answering any questions related to the study and its protocol, the
26 223 investigator will verify inclusion and exclusion criteria and obtain signed informed consent
27 224 form in line with current regulations (from both parents and children ≥ 13 y.o.). After
28 225 successful recruitment, study procedures will be initiated. Simplified patient's course in the
29 226 clinical trial is demonstrated in Figure 1.

33 227 [FIGURE 1]

34 228 Each patient will begin the Trial starting with the enrollment appointment, followed by a
35 229 baseline assessment by a diabetologist and a psychological evaluation. At this stage, all trial
36 230 participants will be provided with Sponsor-funded devices, including pre-configured tablets
37 231 with appropriate telecommunication software and prepaid internet access, wrist
38 232 accelerometers, and blood pressure monitors. Additionally, willing patients who did not
39 233 qualify for reimbursement will be provided with continuous glucose monitoring (CGM)
40 234 sensors and receivers and instructed in their use.

41 235 Next, the patient's parents/legal guardians will participate in a PT program of 10 themed
42 236 online workshops (90 minutes long) led by psychotherapists and supplemented with
43 237 homework and educational materials. PT aims to provide immediate educational and
44 238 behavioral support for the child's caretakers by educating them about ADHD and providing
45 239 tools and skills to understand and modify the child's behaviors and was demonstrated to
46 240 strengthen family bonds and improve adherence to future pharmacotherapy. To successfully
47 241 complete this phase of the Trial, participant's guardians must participate in at least 8 meetings
48 242 – with a possible revisit of the missed ones in another cycle.

49 243 After completion of PT, each participant will repeat the psychological evaluation to assess the
50 244 effects of PT intervention alone on ADHD symptoms severity. Those with sustained clinically-
51 245 significant ADHD symptoms will be qualified for pharmacological intervention. Possible
52 246 contraindications for pharmacotherapy will be assessed during the next diabetological visit.

247 The add-on procedures will include urine tests (pregnancy and panel test for substance us),
248 ECG with QT segment assessment (to exclude longQT syndrome) and ophthalmological
249 consultation (to exclude glaucoma). Subsequent and final assessment and qualification will
250 be performed by psychiatrist during an online consultation. Afterward, each participant
251 starting pharmacotherapy will be randomized using a digital randomization system to receive
252 either MPH or LDX as the first drug.

253 The dose will be optimized during up to four biweekly psychiatric consultations. After the
254 maximum tolerated dose is established, patients will continue pharmacotherapy for 6
255 months. During that time, treatment safety and efficacy will be evaluated twice - after first 3
256 months by psychological and diabetes care team's evaluation (with small dose adjustments
257 allowed) and after full course (6 months) of therapy. On-demand psychiatric consultations
258 will be allowed. In addition, during both diabetological visits each participant will donate a
259 dry blood sample for evaluation of the concentration of an allocated drug, and another
260 sample will be self-collected on the day of the final psychological assessment for that arm to
261 ensure that endpoint measurements are not biased by incidental non-adherence. After the
262 last evaluation, participants will return the unused drug to their diabetes care centre and will
263 begin a wash-out period.

264 Qualification for the second arm of pharmacotherapy will be based on the same procedures
265 and consultations which will be performed in parallel with the last diabetological assessment
266 in the first arm. Final switch and start of the second drug (LDX or MPH) will be based on
267 psychiatrist decision. Dose adjustment, safety and efficacy monitoring will follow the same
268 procedures over the next 6 months. Schedule of the Trial's procedures was presented in Table
269 1.

[TABLE 1]

271 At the end of patient's participation in the Trial, all the Sponsor-funded devices will be
272 returned, and the last safety and efficacy interview will be performed. All the patients will
273 receive further treatment recommendations at NHF facilities.

274 **Randomization**

275 The starting drug will be determined using block randomization stratified by the trial centre in
276 a 1:1 ratio between MPH and LDX as the first drug. The risk of randomization or protocol
277 breakage error will be minimized by using a user-friendly "Randomizer" IT tool provided by
278 the Sponsor, integrated with the eCRF. In the event of unexpected randomization difficulties
279 (e.g., lack of internet access or other technical problems), centre's trial-coordinator may
280 request randomization via backup randomization list available only for sponsor's
281 representative, re-randomization or patient's withdrawal.

282 **Blinding**

283 The participant allocation is open both to the participant and their guardians as well as their
284 attending physician (diabetologist and psychiatrics alike). However, the people assessing the
285 primary outcome (i.e. ADHD symptom severity) will be blinded to the allocation and operating
286 independently from the care centres. No exceptions or unblinding options are planned for

287 those researchers as their assessment serves mostly research purpose, and data collected by
288 them are reviewed by unblinded clinicians.

289 **Endpoints and analysis**

290 The **primary endpoints** of the Trial are:

- 291 1. Efficacy, defined as change in the intensity of ADHD symptoms ("inattention" and
292 "hyperactivity/impulsivity" measured by Conners 3 questionnaire) compared between
293 LDX vs. MPH.
- 294 2. Safety, defined as frequency of MedDRA-defined adverse events for both drugs.

295 For each participant, we will calculate the difference in questionnaire scores ("inattention"
296 and "hyperactivity/impulsivity") at the end of each arm versus the initiation of drug therapy
297 (before first drug). Separate comparisons will be made for each subscale and informant
298 (guardian/child).

299 Safety analysis will report the number of recorded events by type and severity and the
300 incidence rate (the number of events divided by the number of patient-months of
301 observation).

302 The **secondary endpoints** of the Trial are (all compared between LDX and MPH arms):

- 303 1. Diabetes control, as measured by HbA1c and CGM-derived time in target range, mean
304 sensor glucose, and coefficient of variation, before and after treatment with each of
305 investigated drugs;
- 306 2. General and diabetes-related quality of life (measured with PedsQL QoL and diab
307 questionnaires), before and after treatment with each of investigated drugs;
- 308 3. Number and percentage of trial participants that achieved improvement of ADHD
309 symptoms (Conners 3 "inattention" and "hyperactivity/impulsivity") defined as 33%
310 reduction in scale values compared to baseline.

311 The **exploratory endpoints** of the Trial are:

- 312 1. Difference between LDX vs. MPH in school attendance during the month preceding the 6-
313 month drug evaluation;
- 314 2. Difference between LDX vs. MPH in physical activity (daily steps, % of time in moderate-
315 to-vigorous physical activity) and sleep (duration, latency, efficiency) indices;
- 316 3. Differences between baseline assessment and after PTBM completion concerning: in
317 ADHD symptoms severity (Conners 3 "inattention" and "hyperactivity/impulsivity"),
318 HbA1c and CGM-derived glycemic control (time in range, mean sensor glucose, coefficient
319 of variation);
- 320 4. Difference between LDX vs. MPH in frequency (number of events per patient-months) of
321 acute diabetes complications (severe hypoglycemia, ketoacidosis) and hospitalizations,
322 and number of days spent in inpatient care (number of days per patient-months).

323 **Tools and parameters used during the Trial**

324 During in-patient visits in the Trial, standard procedures will be performed, including
325 anthropometric, heart rate, and blood pressure measurements. Applicable values will be
326 referenced with Polish percentile charts.

327 ADHD symptoms will be measured using The Conners' Rating Scales (The Conners 3.0 scales,
328 Polish version) completed by parents (Conners 3.0-P) and children (Conners 3.0-
329 SR). The Conners' Rating Scales are validated and most commonly used tools to assess
330 difficulties in children and adolescents with ADHD in research and clinical settings worldwide.
331 The Polish version of Conners 3.0 has proven high psychometric reliability and validity. In the
332 Trial, we will focus on changes in content scales of "Inattention" and
333 "Hyperactivity/Impulsivity", core two domains of ADHD symptoms by DSM5²⁹.

334 Diabetes control will be assessed using HbA1c measured in local laboratories using methods
335 concordant with the NGSP program. Moreover, patients will be instructed to use continuous
336 glucose monitoring (CGM) according to their leading physicians' recommendations and
337 generated data will be collected during diabetes check-ups. In Poland, CGM is reimbursed in
338 the form of intermittently-scanned CGM, with possible extension into real-time CGM for
339 those with impaired awareness of hypoglycemia. If available, CGMs will be linked with
340 appropriate devices: insulin pumps, CGM readers, mobile phones. CGM data will be backed
341 up and processed using GlyCulator 3.0 platform³¹. For wrist accelerometer data,
342 manufacturer-provided software will be used to collect the data for further analysis.

343 Patient's quality-of-life (QoL) will be measured using the Pediatric Quality of Life Inventory
344 3.2 Core (PedsQL QoL) and Diabetes Module (PedsQL diab)³². The PedsQL is the most common
345 tool to measure QoL in the pediatric population. The PedsQL Diabetes Module allows focusing
346 on T1D-specific issues, especially relevant for the ADHD interaction with T1D self-control.
347 PedsQL QoL and diab have been translated into Polish and validated for academic and
348 commercial use.

349 During the drug dose-optimization period, patients will be tasked with performing self-
350 assessment, including self-monitoring of blood pressure using automated monitors, diabetes
351 monitoring with CGM, and activity monitoring using a wrist accelerometer. Blood pressure
352 monitors data will be periodically uploaded into a central data repository integrated with
353 electronic case report forms (eCRF), while wrist accelerometry will be stored and analysed at
354 the Trial completion. CGM data will be backed up on in-patient clinic visits using appropriate
355 software in each centre.

356 **Statistical analysis**

357 The primary outcome will be compared between the LDX and MPH group using paired t-tests
358 and multivariable regression models to account for clinical covariates. Sensitivity analysis will
359 be performed for primary and secondary endpoints for the subgroup of patients with no
360 imputed data.

361 For each intervention, the % of reported adverse events will be reported with the relevant
362 statistics for paired comparisons (Chi², p), and for the entire table (T_{MB} , p). The incidence rates
363 for individual adverse events will be compared with appropriate statistical tests (Poisson test

364 or equivalent). In addition, each type of event will be compared using the McNemar test, and
365 the frequencies of different events using the McNemar-Bowker global symmetry test.

366 Treatment safety will be assessed and reported following standard procedures and coded
367 using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and WHO severity
368 scale, and recorded in eCRF.

369 Safety and efficacy endpoints will be analysed using data from patients who completed both
370 planned treatments, independent of potential protocol deviations (i.e., population "as
371 treated"). Data of patients lost to follow-up will be filled in on the basis of last-observation
372 carried forward, provided that they have at least one complete timepoint of outcome
373 measures on the current treatment. Patients with deviations from protocol leading to no
374 outcome data will not be included in efficacy analyses.

375 The secondary and exploratory endpoints will be evaluated using the appropriate statistical
376 methods for either continuous (paired t-test, linear regression) or nominal variables
377 (McNemar test). Interim analyses were not planned within this study.

378 **Sample size estimation**

379 To our knowledge, at the time of planning this Trial, no trial with equivalent design and
380 outcome measures in this population was published. Thus, we calculated the sample size to
381 allow for detection of a moderate difference (0.33 standard deviations) difference in score
382 changes between LDX vs. MPH for the key Conners 3 measures³³. Such difference was deemed
383 clinically-impactful by the clinical team designing the trial. To estimate the sample size, we
384 assumed significance threshold of $\alpha=0.05$, the statistical power of 80%. The risk of
385 applying multiple tests (each scale in each type of responder – four in total) was assessed as
386 minimal due to high intercorrelations among those measures. As such, no alpha adjustment
387 was planned. Such assumptions yielded the minimum number of participants of 89 (rounded
388 to 90). The risk of drop-out during pharmacotherapy was assessed as considerable (~33%)
389 due to the challenging population of interest (children with ADHD and T1D, with ADHD
390 possibly present in parents) and known side effects of tested medications. Thus, the target
391 number of pharmacologically-treated children was planned at 135, and 150 recruited given
392 that up to 10% might be disqualified from pharmacotherapy due to drug contraindications or
393 considerable improvement after PT. Assuming recruitment success at 80% (considerable
394 benefit for patients, access to a drug unavailable in Poland, coordinated diabetes and
395 psychiatric care), we estimated that 190 children that should be approached. Based on the
396 general prevalence of ADHD in the pediatric population, the number of patients with T1D to
397 screen for ADHD would be at least 4000 – which was a number of patients supervised by the
398 4 Trial centres.

399 **Data entry and storage**

400 Patient data collected during the clinical Trial will be stored within the electronic trial
401 documentation database, following appropriate regulations, with data access provided to
402 appropriate trial personnel. Reported, presented, and published data will be anonymized. The
403 clinical trial records will be stored for 25 years after trial completion.

404 **Trial monitoring**

405 Trial monitoring will follow adequate international and national clinical trial regulations.
406 Sponsor's representatives will visit each site, discuss the clinical trial course, review and
407 validate relevant records, and verify all reference centres' that partake in the clinical trial.
408 National regulatory authorities may request access to research documentation, source
409 documents, research personnel, and facilities. The Sponsor will be notified of any centre's
410 audits by regulatory agencies, and copies of audit reports will be transferred accordingly.

411 **Ethics and dissemination**

412 **Ethical considerations**

413 The clinical trial follows principles of the Helsinki Declaration, current Good Clinical Practice
414 guidelines, and other applicable regulations. The clinical trial has been registered in European
415 Union Drug Regulating Authorities Clinical Trials Database (no. 2022-001906-24) and in
416 ClinicalTrials.gov (NCT05957055). The clinical trial was approved by the appropriate bioethical
417 committee (agreement no. RNN/142/22/KE), and the Polish Office for Registration of
418 Medicinal Products, Medical Devices and Biocidal Products (UR/DBL/D/263/2022). All
419 participants of the clinical trial are insured within the appropriate insurance agreements
420 (policy no. COR233280) and signed informed consent forms from them and their parents will
421 be collected before trial procedures. All changes in the Trial are subject to ethical and
422 regulatory review before their incorporation into the clinical trial.

423 **Safety during and post intervention**

424 Before the intervention, the treatment of coexisting diseases will be recorded in the eCRF and
425 continued as is or appropriately modified by the respective specialist. All adverse events will
426 be documented in the electronic trial documentation using MedDRA v24.1 and graded using
427 applicable WHO standards, with SAE reported within 24 hours since the occurrence and
428 evaluated by Safety Monitoring Team (SMT). In case of a SUSAR, the SMT follows the Council
429 for International Organizations of Medical Sciences forms and reports it to appropriate
430 authorities within 15 days (or 7 in case of threat to the life or death of the patient) from
431 receiving the report, following the data transfer procedure with the applicable law. The SMT
432 will provide an annual patient safety report throughout the clinical trial, including appropriate
433 information on treatment safety. The Sponsor holds the right to pause or discontinue part of
434 the trial, the entire trial, or the participation of an individual patient.

435 After trial completion, all the patients will receive further treatment instructions, prescription
436 for ADHD treatment and referral to appropriate health provider facilities. Reference
437 diabetology centres will provide continued diabetes care under NHF.

438 **Dissemination plan**

439 Results will be submitted for publication in leading international scientific journals in diabetes
440 care, endocrinology and psychiatry. Results will also be shared during relevant national and
441 international congresses and conferences. The cooperation between the Sponsor and patient
442 organization (affiliation 13) will be continued after the Trial's completion to increase
443 awareness of the impact of psychiatric diseases in patients with T1D.

444 **Discussion**

445 Despite the favorable opinion of the Polish Agency for Health Technology Assessment and
446 Tariff System, LDX is still unavailable for Polish patients outside this clinical trial. We will
447 provide data collected during this Trial for consideration of the Agency, to promote discussion
448 about the availability of LDX and advocate for it being widely accessible (if not reimbursed).
449 We will also perform a specific cost-effectiveness analysis for the particular population of
450 children with ADHD and T1D, and investigate possible costs and benefits of considering LDX
451 as a first-line treatment in this group of patients, justified by the system savings provided by
452 possibly-improved diabetes control.

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54 564 **Author contribution:** AM, JC, HKK, WF, AB, KB – written the article, prepared the clinical
55 565 trial protocol; WF, AB, AM, KB – supervised the clinical trial registration; EK – translated the

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3 566 clinical trial protocol and written the supplementary materials; BM, ASz, ACh, PJCh, MM, IM,
4 567 AK, TW, WF, AB – consulted the manuscript and the clinical trial protocol; MZ –supervised
5 568 patients consultation of the clinical trial. All authors reviewed the results and approved
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8 569 the final version of the manuscript. We comply to the ICMJE guidelines.

9
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13 572 **Competing interest statement:** No competing interests to declare.
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573 **Table 1.** Study schedule. The order of treatment (A/B) will be decided at randomization (allocation step). Names of visits corresponding to Figure 1 are
 574 included.

		STUDY PERIOD										
		Enroll	PT	Allocate	Post-allocation							
DURATION		1 week	10-22 weeks	1 week	First treatment (6 months)				Second treatment (6 months)			
ENROLLMENT	Eligibility screen	X		X				X				
	Informed consent	X										
	Randomization (to A/B)			X								
INTERVENTION	Parent training in behaviour management		X									
	Cross-over	MPH			A	A	A	A	B	B	B	B
		LDX				B	B	B	B	A	A	A
ASSESSMENTS	Conners 3, PedsQL questionnaires	Psychological evaluation 1		Psychological evaluation 2		Psychological evaluation 3		Psychological evaluation 4		Psychological evaluation 5		Psychological evaluation 6
	Diabetes control (HbA1c, CGM)	Diabetological visit 1		Diabetological visit 2		Diabetological visit 3		Diabetological visit 4		Diabetological visit 5		Diabetological visit 6
	Anthropometric, BP, HR measurement											
	Urine tests, ECG with QT segment assessment, ophthalmologic consultation											
	Psychiatric consultation			LDX/MPH qualification	Dose optimization		*Additional dose adjustment		Dose optimization		*Additional dose adjustment	Referral to care under National Health Fund

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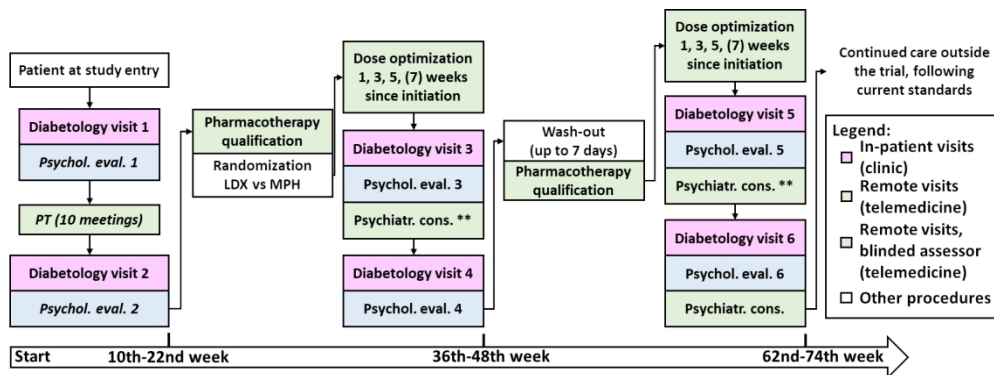


Figure 1. Simplified study design flowchart. PT – parental training, LDX – lisdexamphetamine, MPH – methylphenidate. ** - if needed on-demand consultation

315x117mm (150 x 150 DPI)

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Supplementary File 1: model consent form and other related documentation given to participants and authorised surrogates

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Information for the parent/legal guardian

Information for the parent/legal guardian

LAMAIInDiab - lisdexamfetamine vs methylphenidate for pediatric patients with ADHD and type 1 diabetes - a randomized crossover clinical trial

Study sponsor: Medical University of Lodz

Primary researcher:

Research facility (full name, address, telephone):

Researcher:

Researcher's phone number:

Patient number: _____

Preface

Dear Parent/Legal guardian,

We are contacting you because your child is 8-16.5 years old and suffers from type 1 diabetes (T1D) and attention-deficit hyperactivity disorder (ADHD). This makes them eligible for participation in the "LAMAIInDiab" clinical trial, which aims to improve ADHD therapy and, indirectly, diabetes control. We would like to invite you to participate in this study. The following information will help you understand the purpose of the study and how your participation might look. Please read it carefully. You can also discuss your child's participation in the study with family, friends, or other physicians outside of the study team. We encourage your children to be included in the discussion and decision-making process to the extent of their capacity. If you have any doubts or questions, ask your doctor for clarification.

The study you are invited to is a non-commercial clinical trial sponsored by the Medical University of Lodz, and funded by a Polish government institution, called the Medical Research Agency (ABM). The study is non-commercial, which means that its sponsor cannot make financial profits related to the conducted trial - including applying for registration or marketing authorization of a drug or using the results of the study for marketing purposes. However, these results can be used to change everyday clinical practice and improve the quality of treatment and patients' lives. We intend to include 150 children in the study.

Introduction

The LAMAIInDiab study focuses on two chronic diseases: type 1 diabetes (T1D) and attention-deficit hyperactivity disorder (ADHD). Diabetes is a disease that, as you know very well, requires frequent control of the child's blood sugar level and therapeutic decisions to be made many times a day: calculation of insulin doses, corrective doses, administration of carbohydrates, etc. Some of these decisions are made by you as a Parent/Legal guardian, but over time, more and more of them will belong to your child.

ADHD, on the other hand, is a disorder that makes a child easily distracted by external stimuli, have trouble concentrating on one activity, forget about daily tasks or finish work that has been started. It is a common disorder, affecting about 5% of children according to current research – although only one-fifth of them are diagnosed. If left untreated, it can lead to school difficulties as well as make it

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3 69 much harder to manage diabetes on a daily basis. Forgetting to measure sugar levels, frequent
4 70 mistakes when counting carbohydrates, or missed meals/insulin boluses - some of these events may
5 71 be related to your child's additional illness and are neither his nor your fault. ADHD coexisting with T1D
6 72 increases the risk of life-threatening acute complications of diabetes, frequent hospitalizations, and
7 73 long-term, life-shortening chronic complications. Untreated ADHD can lead to complications in the
8 74 form of poorer school performance, aggressive and antisocial behavior, anxiety and depression
9 75 disorders, problems with psychoactive substance abuse, and also increases the risk of accidents and
10 76 deaths due to them. As part of the LAMAIinDiab study, we want to provide your child with the best
11 77 ADHD treatment in accordance with current guidelines, including access to drugs absent on the Polish
12 78 market, as well as adapted to diabetes therapy. We believe that proper treatment of ADHD will not
13 79 only improve the quality of your child's life but also make it easier for him to control diabetes.

17 80 **What is the standard of ADHD treatment - and how can your child benefit from participation in a**
18 81 **clinical trial?**

20 82 There are two main strategies to treat ADHD. The first one is educating parents/legal guardians on how
21 83 to effectively deal with child's difficult behaviors and support them in coping with the disorder. The
22 84 other, crucial element is taking medications that help reduce the symptoms of ADHD, i.e. improve
23 85 attention and facilitate impulse control. In Poland, there are currently several drugs registered and
24 86 available for the treatment of ADHD in children, with methylphenidate (MPH) being one of the most
25 87 commonly used.

28 88 Unfortunately, combining drugs used to treat ADHD with diabetes therapy is difficult, and few doctors
29 89 are able to reconcile the two therapies. Moreover, both in Poland and in the world, there are no
30 90 specific guidelines for the treatment of ADHD in the particular group of patients with T1D. As a result,
31 91 the therapy, including the choice of drug, is most often based on general guidelines as well as individual
32 92 assessment and clinical experience of the doctor. For this reason the metabolic control of diabetes,
33 93 which is so important for your child, is rarely taken into account when assessing the effectiveness and
34 94 effect of drugs in ADHD.

37 95 LAMAIinDiab is designed to provide your child with care delivered by experts who are familiar with both
38 96 diseases. Your child will be under the care of a well-coordinated team, which will also include you as
39 97 parents/legal guardians. In addition, as part of the study, we will provide your child with access to a
40 98 new ADHD drug, lisdexamfetamine (LDX). It is a drug with proven safety and high efficiency, but not
41 99 available on the Polish market. During the study, you will be able to assess which of the tested drugs
42 100 (LDX or MPH) works better in treating your child's ADHD. Your child's participation in the study will
43 101 ensure that they receive the best possible of care and will allow us to create standards which will
44 102 hopefully improve the care of children with ADHD and T1D throughout Poland in the future.

47 103 **What is a clinical trial, and why are such studies needed?**

49 104 Research into the optimal treatment of ADHD has been ongoing for 75 years. New drugs, tested all
50 105 over the world, give children hope for better functioning. These are difficult studies to conduct because
51 106 they require children, as well as their parents, to take some risks and invest trust in the treatment plan
52 107 prepared by the research team. Often the new treatment turns out to be better than the old one - but
53 108 not always. It is clinical trials like this that tell us what works well - and what needs to be improved.
54 109 People participating in clinical trials, including children and adolescents, are treated according to
55 110 specific rules, the so-called Research Protocol. In addition, they are closely monitored to ensure that
56 111 the treatment is safe and effective.

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3 112 In the case of people with T1D and ADHD, such studies do not yet exist - so we do not know what
4 113 treatment might be best for your child. That is why we want to ask you for your help and participation
5 114 in the LAMAIinDiab study to help test two drugs - methylphenidate (MPH) and lisdexamfetamine (LDX).
6 115 Both are known, safe, and effective drugs in the treatment of ADHD - but we do not know which one
7 116 will be better for your child and how exactly their use can help in the treatment of T1D. Therefore, if
8 117 your child takes part in the study, he/she will receive both of these medicines in a random order. This
9 118 is the first study that will allow us to answer many questions, but above all, provide your child and
10 119 others struggling with this problem with the best possible therapy! The protocol of this study was
11 120 designed by physicians and specialists in both diabetes and ADHD treatment – in part also from your
12 121 Diabetes Clinic.

16 122 **Purpose and course of the study**

17
18 123 The aim of the study is to compare the effectiveness of LDX and MPH in reducing ADHD symptoms in
19 124 a child, as well as to assess the effect of the treatment on T1D control and the child's quality of life.

20
21 125 If you choose to have your child participate in the study, you will be asked to sign a document called
22 126 the Informed Consent Form. This document should be signed by both Parents/Legal guardians taking
23 127 care of the child. Remember to discuss all issues related to the child's participation in the study
24 128 together and with the child to the extent of their understanding. If you have any questions or concerns,
25 129 please ask any of the researchers and we will try to answer them to the best of our ability. In addition,
26 130 girls who could become pregnant and who are sexually-active will be asked to use contraception
27 131 throughout the period of participation in the study. Those who have not started engaging in sexual
28 132 activities will be asked to maintain sexual abstinence.

29
30
31 133 Remember that the consent for the child's participation in the study must be signed by both parents,
32 134 so please - if you can, consult and agree on this matter before visiting the Diabetes Clinic. In the case
33 135 of children from 13 years of age, their signature is also required. If you all consent to your child's
34 136 participation in the study, but it is not possible to collect all signatures (e.g. due to the absence of one
35 137 of the parents at the appointment), we will ask the absent person for verbal (telephone) consent in
36 138 the presence of witnesses - and to sign the document during the next appointment. If one of the
37 139 parents is permanently absent or deprived of parental rights, the consent of one parent supported by
38 140 appropriate documents is sufficient. In the event of disagreement between the legal guardians or legal
39 141 guardians and the child, the case may be settled by the guardianship court.

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41
42 142 After agreeing to participate in the study, your child will be required to follow the planned treatment
43 143 protocol and doctor's recommendations - please help them in this by explaining the next steps of the
44 144 study and encouraging to participate in study visits. You and your child will also be required to report
45 145 all disturbing events observed in your child such as unwelcome symptoms or deterioration of health,
46 146 even minor ones such as colds, headaches, and sleep problems. Keeping accurate records of these so-
47 147 called adverse events helps us to ensure that the treatment proposed in the protocol is safe.

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50 148 Treatment in the study will take place in your current diabetes clinic - and at home, using online
51 149 appointments. This way, you will be in constant contact with us and will not have to travel further than
52 150 your Diabetes Clinic.

53
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55 151 After starting participation in the study, your child will be invited for the first appointment to the center
56 152 - i.e., your Diabetes Clinic. During it, the child will undergo a full physical examination, and his/her
57 153 health and development will be assessed, as well as diabetes control - similar to a standard diabetes
58 154 appointment. A drop of capillary blood will also be taken from child's finger to measure glycated
59 155 hemoglobin.

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3 156 During this appointment, you will be provided with the equipment necessary to participate in the
4 157 study. First, you will receive a tablet with internet access and applications necessary for full
5 158 participation in the study. It will be lent to you for the entire duration of the study based on appropriate
6 159 agreement, and the transmission of internet data will be financed from the research funds. This tablet
7 160 will be used to make remote appointments with certain researchers. You will also receive an
8 161 accelerometer to measure your child's activity. It will be a device in the form of a wrist watch, which,
9 162 uses hand movements to estimate the number of steps taken, the intensity of physical activity, and
10 163 the quality of sleep. **We do not require your child to wear the accelerometer for the entire duration
11 164 of the study** - we will only ask you to wear the watch three times during the entire study, each time
12 165 for 2 weeks. Importantly, we ask that your child wears it also at night because we want to assess how
13 166 the treatment affects not only daily activity but also the length and quality of sleep. The exact
14 167 information on the use of the accelerometer will be provided to you by the researcher when dispensing
15 168 the equipment. The equipment you will receive for the purposes of the study will be lent by the
16 169 Sponsor on the basis of a separate lending agreement signed by you - and should be returned at the
17 170 end of the child's participation in the study. The rented equipment will have a manufacturer's warranty
18 171 and valid insurance, but please treat it with care like any medical device, e.g., an insulin pump.

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23 172 We would also like your child to use a Continuous Glucose Monitoring (CGM) system while
24 173 participating in the study. As you probably know, this is a small subcutaneous device that resembles
25 174 an insulin pump infusion set. It continuously measures the glucose concentration in the subcutaneous
26 175 tissue and uses it to estimate blood glucose. It is possible that your child already uses some kind of
27 176 CGM system and it is a daily routine for you. If this is the case, participation in the study does not
28 177 change anything for you, we ask that you use CGM regularly and we will use the data collected by the
29 178 system to assess your child's diabetes control during subsequent appointments. If your child has not
30 179 used CGM before or is not currently using it - we would like to offer him the opportunity to use it during
31 180 his participation in the study. In this case, your center will provide you with free CGM sensors sufficient
32 181 to monitor your child between appointments, and your doctor will tell you how to use them. We
33 182 strongly encourage you to use CGM, although it is not mandatory in this study - we believe that it will
34 183 make it easier for you to control diabetes and will ease the burden of finger pricking and capillary blood
35 184 glucose measurements.

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39 185 Then, within a few days since your first appointment in the center, you will have your first
40 186 teleconsultation with a researcher outside of your Diabetes Clinic. During it, the investigator will
41 187 perform two surveys with you. The first is the detailed Conners 3 questionnaire, which assesses the
42 188 intensity of ADHD symptoms. The examination will consist of asking the child and then the parent/legal
43 189 guardian a series of questions assessing the daily functioning of the child. The second questionnaire
44 190 (PedsQL) will assess the child's quality of life, both general and diabetes-related. Here, too, the
45 191 researcher will ask you and your child a number of questions. The entire examination should not take
46 192 more than 30-40 minutes. This study and all the questions asked during it will be repeated in
47 193 subsequent teleconsultations of this kind - and are extremely important for the success of the study.
48 194 Therefore, we ask for your patience and understanding, as well as to explain to your child why we ask
49 195 the same questions from time to time. We do this to reliably assess the change in the severity of the
50 196 child's ADHD symptoms and his quality of life at the beginning of the study and in the subsequent
51 197 stages of treatment - which will allow us to compare the effectiveness of the interventions and
52 198 medications used.

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57 199 After this initial assessment, we will ask you to participate in training for parents/legal guardians of
58 200 children with ADHD. Its goal is to familiarize you with ADHD as a disorder and to teach you how to
59 201 work with your child on correcting problematic behaviors. Meetings will take place online in groups of

several people, once a week for 10 weeks. Each meeting will last approximately 90 minutes. The meetings will be conducted by an experienced specialist in psychoeducation who will answer your questions about ADHD and show you how to work with your child. In addition, you will have the opportunity to talk and exchange experiences with parents of other children suffering from ADHD and T1D. After each meeting, you will also receive a set of educational materials and tasks to work on at home. At least one parent/legal guardian of a given child should attend each meeting. To proceed to the next stages of the study, you must complete at least 8 meetings in the series. If more than 2 meetings are missed, you can retake them in the following 10-week cycle.

After the end workshops, you will participate in another teleconsultation assessing the symptoms of ADHD and the quality of your child's life. If the symptoms of ADHD are still detectable during this examination and at the appropriate level, the child will be eligible to receive pharmacotherapy. Remember that most children with ADHD require the use of medication, and education (such as a completed series of workshops) is aimed at improving their performance - so the risk that the child will be disqualified from the study at this stage is very low.

Next, we will invite you for another appointment at your diabetes care center. Apart from full physical examination, assessment of the child's development and diabetes control, and diabetologist consultation, your child will undergo: ophthalmologist consultation, ECG, laboratory tests (blood count, HbA1c concentration, thyroid hormones). Their aim is to check for possible contraindications to the studied drugs – clinically-relevant heart disease, glaucoma etc. There is small risk that at this stage your child might be disqualified from pharmacological treatment if the tests and consultations reveal important health problems. In such circumstances, continued participation in the study and use of studied medications could not be safe for your child. In such case (and in any case when your child finishes their participation in the study, either prematurely or not) you will receive information about places you can receive ADHD treatment within public healthcare.

During this appointment, urine samples will also be taken from your child for a drug screening test and (in the case of girls) a pregnancy test. Both the use of psychoactive substances and pregnancy are hard contraindications to the use of the tested drugs.

During the appointment, you will also receive a blood pressure monitor for automatic blood pressure measurements at home. After the start of pharmacotherapy, we will ask you to perform (or supervise) regular blood pressure measurements in your child, as the tested drugs may slightly increase it.

After the appointment at the center, there will be a teleconsultation with another investigator: a resident physician or a specialist in child and adolescent psychiatry. During this appointment, the investigator will qualify your child, based on the medical history and available test results and consultations, to receive pharmacotherapy in a clinical trial. During the study, we will evaluate the effectiveness of two drugs: MPH in a long-acting form and LDX. Your child will take both medicines sequentially: methylphenidate for 6 months first, then lisdexamfetamine for 6 months, or vice versa (lisdexamfetamine first and then methylphenidate).

The order of drugs used in the study will be determined randomly – this makes the results more reliable. After drawing the first drug, the doctor will inform you and your child about its exact characteristics, method of administration and will answer your questions and doubts.

After the end of the 6-month treatment with one of the drugs, a separate qualification will take place before starting the other. The risk that your child will be disqualified from the study at this stage is very low because both drugs have the same contraindications - we just want to check if anything significant has happened in the child's medical history after half a year of treatment.

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3 246 Once treatment has started, your child will receive a predetermined starting dose, which will then be
4 247 adjusted to meet his/her individual needs over the next 5 weeks. After 1, 3, and 5 weeks since starting
5 248 the drug, you will participate in further online appointments with the same investigator, who will
6 249 assess the effectiveness of the current dose based on information from you and your child and adjust
7 250 it if necessary.
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10 251 During the dose adjusting process (for the first 5 weeks of treatment) we will ask you to measure your
11 252 child's blood pressure every two days, two times a day (in the morning before school and after school
12 253 between 2-6 pm,), and to observe behavior and appetite child.

13
14 254 After each of these appointments (including the first), you will receive a prescription for the study drug,
15 255 which you will have to take to your Diabetes Center. Due to the legal regulations of clinical trials, the
16 256 drug can only be collected in the study center.

17
18 257 We hope that during these appointments we will be able to determine the most optimal dose of
19 258 medicine for your child, but if not, an additional appointment after another two weeks will be possible
20 259 to ensure that your child is being treated in the best possible way.

21
22
23 260 During this time, we will ask you, as the child's guardian, to regularly collect the medicine from the
24 261 Center and return unused medicines or empty packaging of the studied drugs.

25
26 262 Once we have determined the right dose of medicine, your child will take it for 6 months (so the next
27 263 21 weeks), every day, at a fixed dose. During this time, we will ask you to measure the child's blood
28 264 pressure once a week, on a fixed day of the week, at a fixed time (it may be a weekend).

29
30 265 After 3 months, we will invite your child for a check-up appointment at the Center, during which we
31 266 will carry out standard diabetic consultation procedures: physical examination, including weight,
32 267 height, and blood pressure measurements, medical interview, assessment of diabetes control,
33 268 capillary blood collection from the finger to measure glycated hemoglobin concentration. In addition,
34 269 we will then collect capillary blood from the finger (4 drops) on a special paper in an amount similar to
35 270 that needed to measure blood glucose with a glucometer. It will then be sent (marked with the number
36 271 of clinical trial participant) to the laboratory in order to measure the concentration of the administered
37 272 drug in a dry blood sample. This will allow us to assess whether the child is using the prescribed study
38 273 drug regularly. At this visit, you will also receive a single home dry blood spot kit and instructions on
39 274 how to use it. This is not very different from measuring your blood glucose with a glucose meter. We
40 275 will ask you to collect a dried blood sample from the child once on a fixed date before the next
41 276 stationary appointment. It is a collection of capillary blood, such a drop as for blood glucose testing
42 277 using a glucometer. At this appointment, you will be dispensed a supply of medicine for the next 3
43 278 months.
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48 279 At the same time, within a maximum of a week from the appointment at the Center, another
49 280 teleconsultation will be held, with the assessment of the intensity of ADHD symptoms (Conners 3
50 281 questionnaire) and the quality of life (PedsQL).

51
52 282 After 6 months from the start of pharmacotherapy, your child will undergo another psychological
53 283 assessment in the form of a teleconsultation- this will be the last assessment of ADHD symptoms and
54 284 quality of life during treatment with a given drug.
55

56 285 Then, we will again invite your child to the appointment at the Center. This time, in addition to a
57 286 diabetes consultation and physical examination, the doctor will conduct the tests necessary to start
58 287 the second drug. Similar to the previous qualification appointment, these will include: an
59 288 ophthalmologist consultation, ECG, and laboratory tests (blood count, HbA1c concentration, ferritin

1
2
3 289 concentration, thyroid hormones). Urine samples will also be taken for a pregnancy test and a drug
4 290 screening test. We will also collect a dried blood spot sample, similarly to the previous visit. After the
5 291 tests are performed, a psychiatric teleconsultation will be held again in order to start the second drug.
6 292 The course of treatment will be identical to that of the first drug (5 weeks of dose selection, stationary
7 293 appointment + psychological assessment after 3 and 6 months).

8
9
10 294 At the end of the study (after completion of pharmacotherapy with both drugs or at any other time in
11 295 the event of withdrawal of consent or disqualification from the study), we will invite you and your child
12 296 to the last appointment at the center, during which the investigator will examine the child, discuss
13 297 recommendations for further care and collect the loaned equipment: tablet, accelerometer, and blood
14 298 pressure monitor.

16 299 **What do I need to know about the drugs used in the study?**

17
18 300 The methylphenidate (MPH) used in the study is an oral extended-release capsule medication used as
19 301 a first-line treatment for ADHD in children. After oral administration of the product, the active
20 302 substance (methylphenidate) is gradually released over the next few hours. Peak blood concentrations
21 303 are reached approximately 6 to 8 hours after taking, after which the blood concentration of
22 304 methylphenidate gradually decreases.

23
24
25 305 Lisdexamfetamine (LDX) is a prodrug, meaning a molecule that becomes an effective drug only after
26 306 being modified by the body. In this case, oral administration of lisdexamfetamine is followed by rapid
27 307 absorption from the gastrointestinal tract followed by hydrolysis to dexamfetamine, which is
28 308 responsible for the drug's pharmacological effect. This gives it a more stable profile and a longer
29 309 operating time (up to 13 hours). It is a new drug, available on the American and European markets for
30 310 several years. Unfortunately, LDX is not currently available on the Polish market.

33 311 **Side effects**

34
35 312 Like any drug, both methylphenidate and lisdexamfetamine have been tested for side effects. The most
36 313 common ones are listed below. Most of them are mild and do not interfere with your child's daily
37 314 functioning. However, if they occur during the study, their severity will be analyzed on a case-by-case
38 315 basis may be an argument to stop child's participation in the study. All side effects during the study
39 316 will be monitored and reported, and your child will be given appropriate help if they experience them.

41 317 **Methylphenidate**

42
43 318 Very common (may affect more than 1 in 10 people)

44
45 319 insomnia, nervousness, headaches.

46
47 320 Common (may affect up to 1 in 10 people)

48
49 321 nasopharyngitis, anorexia, decreased appetite, a moderate decrease in weight gain and height during
50 322 prolonged use in children, emotional lability, aggression, agitation, anxiety, depression, irritability,
51 323 abnormal behavior, dizziness, dyskinesia, psychomotor hyperactivity, somnolence, arrhythmia,
52 324 tachycardia, palpitations, hypertension, cough, pharyngolaryngeal pain, abdominal pain, diarrhea,
53 325 nausea, abdominal discomfort, vomiting, dry mouth, alopecia, itching, rash, hives, joint pain, fever,
54 326 growth retardation with prolonged use in children, changes in blood pressure and heart rate (usually
55 327 increased), body mass reduction.

56
57
58 328 Uncommon (may affect up to 1 in 100 people)

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2
3 329 hypersensitivity reactions such as angioedema, anaphylactic reactions, ears edema, blistering, skin
4 330 peeling, hives, itching, rash, skin eczema, mental disorders, auditory, visual, and tactile hallucinations,
5 331 anger, suicidal thoughts, mood changes and swings, nervousness, tearfulness, tics, aggravation of
6 332 existing tics in the Tourette's syndrome, hypervigilance, sleep disorders, suicide attempts (including
7 333 completed suicide), transient depressive mood, abnormal thinking, apathy, repetitive behavior, hyper
8 334 concentration, sedation, tremor, diplopia, blurring of vision, chest pain, dyspnea, constipation, liver
9 335 enzymes increased, angioedema, bullous conditions, exfoliation, myalgia, muscle convulsions,
10 336 hematuria, fatigue, heart murmurs.

11
12
13 337 Rare (may affect up to 1 in 1,000 people)

14
15 338 mania, confusion, libido disorder, convulsions, choreoathetotic movements, reversible ischemic
16 339 neurological disorders, neuroleptic malignant syndrome (NMS; reports poorly documented, in most
17 340 cases patients also received other drugs. The role of methylphenidate in these cases is uncertain),
18 341 difficulty in accommodation, mydriasis, visual disturbance, angina pectoris, hyperhidrosis, rash
19 342 macular, erythema, gynecomastia.

20
21
22 343 Very rare (may affect up to 1 in 10,000 people)

23
24 344 anemia, leukopenia, thrombocytopenia, thrombocytopenic purpura, cardiac arrest, myocardial
25 345 infarction, inflammation and/or occlusion of cerebral arteries, distal freezing, Raynaud's phenomenon,
26 346 hepatic dysfunction (including hepatic coma), erythema multiforme, dermatitis exfoliative persistent
27 347 drug rash, muscle spasms, sudden cardiac death, blood alkaline phosphatase increased, bilirubin
28 348 increased, platelet count decreased, white blood cell count abnormal.

29
30 349 Not known (frequency cannot be estimated from the available data).

31
32 350 pancytopenia, delusions, thinking disorders, confused states, cases of abuse and addiction have been
33 351 described, more often for immediate-release formulations, cerebrovascular disorders (including
34 352 vasculitis, cerebral hemorrhage, cerebral arteritis, cerebral vascular embolism), grand seizures mal,
35 353 migraine, supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles, chest
36 354 discomfort, very high fever.

37 355 **Lisdexamfetamine**

38
39
40 356 Very common (may affect more than 1 in 10 people)

41
42 357 decreased appetite, weight loss, difficulty sleeping, dry mouth, abdominal pain, headache

43
44 358 Common (may affect up to 1 in 10 people)

45
46 359 uneven heartbeat (palpitations), chest pain (may be a sign of heart disease), agitation, nervousness,
47 360 anxiety, depression, aggression, irritability or mood swings, severe sleepiness, tiredness or
48 361 restlessness, difficulty getting or keeping an erection or changes in libido, dizziness, uncontrollable
49 362 spasms, involuntary muscle movements or tremors, shaking or unusual activity, irregular or rapid
50 363 heartbeat (tachycardia), shortness of breath, nausea, vomiting or diarrhea, constipation, fever or
51 364 sweating, rash, teeth grinding

52
53 365 Uncommon (may affect up to 1 in 100 people)

54
55 366 seeing, feeling, or hearing things that are not there (hallucinations), being over-excited, being over-
56 367 active, having no inhibitions (mania), allergic reactions (hypersensitivity), shortness of breath or
57 368 swelling of the legs (signs of heart disease) talking, feeling depressed, anxious, depressed or restless (
58 369 dysphoria), feeling happy and excited (euphoria), frequent skin picking, uncontrollable muscle spasms

370 or sudden body movements, itching, rash or red itchy patches (hives), blurred vision, dilated pupils,
371 poor blood circulation which causes numbness and whiteness fingers and toes (Raynaud's
372 phenomenon), high blood pressure, metallic taste or changes in taste (dysgeusia), fainting

373 Not known (frequency cannot be estimated from the available data)

374 severe allergic reactions with a rapid drop in blood pressure, shortness of breath and itching/hives
375 (anaphylactic reaction), seeing, feeling, or hearing things that are not there, paranoia, delusions
376 (psychotic symptoms), convulsions (seizures), abnormal heart rhythm, life-threatening irregular heart
377 rhythm (seen on an electrocardiogram), allergic liver damage which may be accompanied by yellow
378 eyes and/or skin (eosinophilic hepatitis), swelling of the skin (angioedema) or a severe rash with
379 blisters on the skin and mucous membranes (Stevens-Johnson syndrome).

380 In addition, if the Research Team obtains new information related to the clinical trial that may affect
381 your child's further participation, you and your child will be immediately informed by the doctors from
382 your facility.

383 **Does my child have to take part in the study?**

384 No, regardless of the consent to participate in the study, your child will remain under constant diabetes
385 care in accordance with the standards of care in Poland.

386 **Are there other alternative treatments available?**

387 Methylphenidate is the first-line treatment for ADHD in children. Other used drugs include
388 atomoxetine, reboxetine, and clonidine, but they are less effective in reducing ADHD symptoms. They
389 may be appropriate in particular cases, e.g. in the presence of methylphenidate intolerance or the
390 presence of additional disorders/diseases.

391 Lisdexamfetamine is currently unavailable on the Polish market.

392 **What medical procedures will be performed in connection with participation in the study and what 393 risks may result from their performance?**

394 Despite the experience of the staff and the diligence of medical procedures, the occurrence of
395 complications cannot be ruled out. The main medical procedures and their possible complications are
396 listed below:

- 397 • **Physical examination:** non-invasive procedure.
- 398 • **Blood sampling:** weakness and fainting after blood sampling, injection site infection,
399 local allergic reactions.
- 400 • **Sampling for dry blood spot testing:** dirtying/infection at the puncture site, local
401 allergic reactions.
- 402 • **Collecting a urine sample for a pregnancy test and a multitest for psychoactive
403 substances:** a non-invasive procedure
- 404 • **Electrocardiography (ECG):** non-invasive procedure.
- 405 • **Blood pressure measurement:** non-invasive procedure
- 406 • **Accelerometer sleep and activity monitoring:** local allergic reactions
- 407 • **Glucose monitoring using CGM:** infections of the skin and subcutaneous tissue at the
408 sensor site, local allergic reactions

409 Prior to each procedure, the study physician will discuss with you the exact course of the procedure
410 and the associated benefits/risks.

411

412 Sample storage (biobanking) and additional tests

413 Samples collected during treatment, such as blood, blood serum, and dry blood drop test strips, will
414 be stored in research centers in Łódź, Gdańsk, Katowice, or Opole. The storage time of patients'
415 biological samples was set at 5 years from the end of treatment. Information about the stored material
416 will be available to you and your parents/legal guardians.

417 Complementary tests should help us better understand the causes of your condition and how your
418 medications work and identify further risk factors. The aim is also to treat patients more effectively
419 according to their individual regimens.

**420 What are my child's responsibilities as a study participant and mine as a participant's
421 Parent/Guardian?**

422 If you consent to your child's participation in the study, it will be your and your child's responsibility to
423 follow the recommendations of the doctor conducting the study (Investigator), and to report any
424 disturbing symptoms regarding the child's health. Certain medications must not be used during the
425 study. Therefore, before participating in this study, the study doctor (Investigator) will check if your
426 child is not taking these medications or has stopped taking them early enough. Some medicines may
427 require dose adjustments. Inform the study doctor (Investigator) before your child starts and/or
428 changes any medications, including over-the-counter medications. The study doctor (Investigator) may
429 decide to withdraw your child from the study for medical reasons (e.g. occurrence of a serious adverse
430 event or a serious adverse reaction to a medicinal product), in the event of non-compliance with the
431 instructions of the doctor conducting the study (Investigator), or for other important medical reasons.

432 Do I have to pay for the medicines my child will receive?

433 The drugs in the study are provided by the Sponsor (Medical University of Lodz) free of charge. It is
434 necessary to collect drugs at research centers designated for this purpose.

435 Your child's participation in the study is completely free and you do not have to incur any costs. You
436 will not be financially compensated for your child's participation in the study, and you will not be
437 reimbursed for time and travel expenses that may be necessary for study site visits.

438 Who can I contact if I have questions or problems?

439 If you have any questions, problems, or concerns about any part of the study, or if you believe your
440 child has been harmed as a result of this study, you may contact the Primary Investigator or your child's
441 study doctor. You can also discuss any doubts or concerns about the study with them at any time. We
442 will do our best to give you a satisfactory answer (please use the contact details at the end of the
443 Information).

444 If you have any questions about your child's rights as a research participant, or any problems that you
445 feel cannot be discussed with the Researchers, you can contact the independent Bioethics Committee
446 that issued a positive opinion about the research. Contact details are indicated below:

447 Bioethics Committee at the Medical University of Lodz
448 Pl. Hallera 18, 90-647 Lodz
449 II floor, room 230
450 phone number: 785 911 596, 42-272-52-43, 42-272-52-44
451 e-mail: bioetyka@umed.lodz.pl

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2
3 453 You can also contact the Patient Ombudsman if you have questions or concerns you would like to
4 454 discuss with someone outside of the research team. Contact details:

5
6 455 Office of the Patient Ombudsman/Patients Rights Office
7 456 Młynarska 46 street
8 457 01-171 Warsaw
9 458 Mon.: 9.00-18.00, Tue-Fri.: 9.00-15.00 or via phone number: 800-190-590 (Mon.-Fri.: 8.00-18.00).
10 459

11 12 13 460 **Clinical trial insurance**

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15 461 Under applicable law, the research Sponsor and the researcher are covered by civil liability insurance
16 462 for damages caused by the act or omission of the insured, which took place during the period of
17 463 insurance cover, in connection with the conduct of the research.

18
19 464 The relevant policy number for this study is: COR285781

20
21 465 A copy of the policy along with the terms and conditions of insurance is at the Principal Investigator
22 466 conducting the study and will be available for inspection.

23
24 467 You can report any damages arising in connection with participation in the study directly to the insurer.

25
26 468 In the event of any damage arising in connection with participation in a clinical trial, the participant is
27 469 entitled to free treatment of the said damage.

28 29 470 **What will happen to the results of the study after its completion?**

30
31 471 After the end of the study, that is, after the last visit of the last participant in the study, the collected
32 472 information will be analyzed, presented at scientific conferences, and published in recognized medical
33 473 journals. The results of the study may be used to change the current ADHD and T1D treatment
34 474 guidelines, as well as to develop new therapies. The identity of the patients who participated in the
35 475 study will remain anonymous.

36 37 476 **What happens to samples taken from my child during the test?**

38
39 477 Blood samples collected during visits and dry blood sample blotting papers that remain after laboratory
40 478 testing will be retained for 5 years after the end of the study in case new therapeutic options become
41 479 available to target specific genetic variants associated with ADHD or diabetes. Urine samples will not
42 480 be stored and will be destroyed. During one of the diabetic blood collection appointments, we will
43 481 collect two additional blood samples from your child for future research projects. They will be marked
44 482 only with your child's Patient number (without identifying data) and then sent to the Medical
45 483 University of Lodz, where they will be stored for a maximum of 5 years. The samples will be used in a
46 484 separate medical experiment and reviewed by the relevant Bioethics Committee.

47 48 49 485 **Who verified the study?**

50
51 486 The study was reviewed and approved for by an independent Bioethics Committee at the Medical
52 487 University of Lodz, which is responsible for ensuring that all study participants are properly informed
53 488 about the risks associated with the study and that the decision to participate is a voluntary choice. The
54 489 President of the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products
55 490 also approved the study.

56 57 58 491 **Will my child's participation in the study be confidential?**

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3 492 Yes. All information collected about your child in connection with the study will be processed in
4 493 accordance with generally applicable law, in particular with Regulation (EU) 2016/679 of the European
5 494 Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the
6 495 processing personal data and on the free movement of such data and repealing Directive 95/46/EC
7 496 (General Data Protection Regulation) (hereinafter: "GDPR") and the Act of 10 May 2018 on the
8 497 protection of personal data. Personal Data is processed only for the purpose of conducting the study
9 498 and to the extent necessary for its implementation, and access by authorized persons (e.g. monitors
10 499 or auditors) to direct medical records will be possible only on the premises of the research center. All
11 500 study data will be pseudonymized and assigned a unique study number (instead of the name and
12 501 surname, the data will only be marked with a code).

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16 502 All detailed information on the principles of processing Personal Data can be found in the Consent
17 503 Form for the Processing of Personal Data.

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505 Informed consent form for participation in a clinical trial

506 **LAMAinDiab – lisdexamfetamine vs methylphenidate for pediatric ADHD patients with type 1**
507 **diabetes - randomized crossover clinical trial**

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509 Patient's name:

- 510 1. I confirm that I have read and understood the **Parent/Legal Guardian Information** regarding this
511 clinical trial. I had the opportunity to read the information provided, ask questions and receive
512 satisfactory answers.
- 513 2. I understand that my child's participation in the study is voluntary, and I can withdraw from it at
514 any time without giving any reason, without affecting the medical care provided and my rights.
- 515 3. I have been informed that the doctor conducting the study (Investigator) may decide to stop my
516 child's participation in the study for medical reasons, as well as in the event of non-compliance
517 with the recommendations
- 518 4. I consent to the researcher's access to my child's medical records prior to the commencement.
- 519 5. I agree that after the end of the study, the information collected will be analyzed, presented at
520 conferences, published in scientific journals, and used to develop new therapies.
- 521 6. I understand that biological samples from my child will be analyzed for the purpose of this study.
- 522 7. I have read and accept the general terms and conditions of third-party liability insurance of the
523 Sponsor and the Investigator.
- 524 8. I undertake to follow the recommendations regarding the clinical trial that will be provided to me
525 by the Research Team.
- 526 9. I have been informed that I will receive a copy of the Parent/Legal Guardian Information and a
527 copy of the Informed Consent Form.
- 528 10. I give my voluntary consent for my child to participate in this clinical trial
- 529 11. Consent to storage of biological material
- 530 You have the option of consenting to the Researchers using samples of biological material collected
531 from your child for storage in research centers in Łódź, Gdańsk, Katowice, or Opole. Whatever you
532 decide, it will not affect your child's medical care. Your child may continue to participate in the study
533 even if you decline.

534 After deciding, please mark the answer with a cross

535 "YES" if you consent to the obtained biological material being stored and/or used to perform optional
536 tests, Or "NO" if you do not wish to keep any samples. YES NO

537

Name and surname of the Parent/Legal Guardian (Capital letters)	Date (handwritten)	Signature (handwritten)
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Name and surname of the Parent/Legal Guardian (Capital letters)	Date (handwritten)	Signature (handwritten)
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Name and surname of the Researcher receiving the Consent (Capital letters or stamp)	Date (handwritten)	Signature (handwritten)
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3 538 Consent form for the processing of personal data of a participant in the **LAMAIinDiab clinical trial -**
4 539 **lisdexamphetamine vs methylphenidate for pediatric patients with ADHD syndrome and type 1**
5 540 **diabetes - randomized crossover clinical trial**

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9 542 Patient's name:

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11 543 I consent to the processing of my minor child's Personal Data in the scope of name and surname, date
12 544 of birth, gender, PESEL number, and data from the shared medical documentation, for the purpose of
13 545 conducting this clinical trial, as well as my Personal Data in the scope of name and surname for the
14 546 purpose of proper processing and documenting the study. I declare that I have been informed about
15 547 the purposes, scope, and conditions of processing Personal Data in accordance with art. 13 GDPR. I
16 548 also declare that I have received a copy of the information clause, which is Appendix 1 to this form.

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Name and surname of the Parent/Legal Guardian (Capital letters)	Date (handwritten)	Signature (handwritten)
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Name and surname of the Parent/Legal Guardian (Capital letters)	Date (handwritten)	Signature (handwritten)
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Appendix 1

Information clause regarding the processing of Personal Data for the purpose of conducting and controlling a clinical trial on "LAMAinDiab - lisdexamfetamine vs methylphenidate for pediatric patients with ADHD syndrome and type 1 diabetes - randomized crossover clinical trial".

According to Art. 13 sec. 1 of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of Personal Data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (hereinafter: "GDPR"), we inform you that:

1. The administrator of the Personal Data provided by you for the purpose of conducting and controlling this clinical trial is the Medical University of Łódź, ul. Al.Kościuszki 4, 90-419 Łódź (hereinafter referred to as: "Sponsor"). These data include both the Patient's Personal Data, i.e. a minor on behalf of whom you gave consent to participate in the study, and your personal data as a legal guardian to the extent necessary for the processing and implementation of the study (hereinafter jointly referred to as: "Personal Data").
2. Contact with the Administrator is possible via the e-mail address iod@umed.lodz.pl. Regardless of the possibility of contacting the Sponsor's Personal Data Protection Officer, any questions can be directed to the Investigator who is conducting the study.
3. The Personal Data provided by you will be processed on the basis of art. 9 sec. 2 letter a) and j) of the GDPR in order to monitor the safety of pregnancy.
4. All Personal Data provided by you will be pseudonymized (instead of the name and surname, the data will be marked with a code).
5. The personal data provided by you will be made available to the Medical Research Agency with its registered office at ul. Stanisława Moniuszko 1A, 00-014 Warsaw, which is the entity financing the study. For the purpose of conducting the test, your personal data may be made available to the Research Center where the test is carried out, to an external monitor, as well as to external laboratories testing samples as part of the test.
6. Access to the data provided by you may also be obtained by authorized persons and bodies, in particular the Bioethical Committee approving the Study, as well as the Sponsor's subcontractors (including external service providers, e.g. providers of technical, ICT services, diagnostic equipment, legal services, inspection services, etc.) or partners, persons involved in conducting the study, in particular, study observers (monitors), auditors, inspectors, doctors, nursing team, as well as national institutions supervising the study, provided that the received data is kept confidential.
7. Based on the personal data provided by you, no decisions will be made in an automated manner and the data will not be subject to profiling.
8. The personal data provided by you will not be transferred to a third country outside the territory of the European Union and the European Economic Area.
9. The Personal Data provided by you for the purposes of monitoring the course of pregnancy safety will be processed for a period of 5 years, and medical documentation - if it was created - for a period of 20 years.
10. You have the right to lodge a complaint to the President of the Office for Personal Data Protection for unlawful processing of Personal Data.
11. You have the right to access the content of Personal Data and the right to rectify, delete, limit processing, the right to transfer data, the right to raise objections, the right to withdraw consent at any time without affecting the lawfulness of processing, which was made on the basis of consent before its withdrawal - within the limits specified in the law.
12. Providing your Personal Data is fully voluntary and has no impact on the implementation of the Research

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Information for the Patient (8-12 years old)

For peer review only

616 Information for the Patient (8-12 y.o.)

617 LAMAIInDiab – lisdexamfetamine against methylphenidate for pediatric patients with attention-
618 deficit hyperactivity disorder and type 1 diabetes – randomized crossover clinical trial

619 Study Sponsor: **Medical University of Lodz**

620 Main Investigator:

621 Study Institution (full name, adres, telefon):

622 Investigator:

623 The telephone number for the primary physician:

624 Patient's number:

625 **Hello!**

626 We are a group of doctors and researchers who are trying to help people with diabetes to manage
627 their disease and enjoy life – some of us you might have met at your Diabetology Clinic. We are
628 reaching out to you because we know that other than type 1 diabetes, you also have attention-deficit
629 hyperactivity disorder, and no one should face such challenges alone! We believe that ADHD treatment
630 may help you feel better and improve your diabetes control. This is why we are inviting you to join our
631 study LAMAIInDiab.

632 At the start, we will show you what ADHD is and how it affects diabetes. Next, we will tell you about
633 how we want to help you. The information pamphlet that you are reading right now is seven pages
634 long. You might find some of it boring or hard to follow. Please, ask us if you are interested in something
635 or if some things are difficult to understand. We will do our best to answer and explain all you find
636 unclear. After completing this pamphlet, you can ask your primary physician any relevant questions.

637 **What is ADHD?**

638 ADHD, or attention-deficit hyperactivity disorder, affects one in 20 people – so it's even more common
639 than diabetes! People with ADHD may find it challenging to sit down and focus on school or while doing
640 their homework. Have you ever forgotten to measure your glucose or made a mistake while counting
641 the required insulin? Or forgot about the meal? This may be because of ADHD.

642 In this study, we want to help you deal with your issues connected to ADHD and type 1 diabetes. In the
643 LAMAIInDiab, with the team of the best clinicians and researchers in Poland, we will try and make it
644 easier for you to control diabetes and ADHD. You may be one of 150 children who will participate in
645 this study!

646 **How do we treat ADHD?**

647 To treat ADHD, you need two things. First, you and your parents/guardians need to learn about ADHD
648 and how to cope with undesired behaviors. The second, very important thing is taking medication that
649 help „calm the storm” of ADHD. This will make it easier for you to achieve your goals. It is challenging
650 to treat ADHD and type 1 diabetes together, so in LAMAIInDiab, you will receive care from experts with
651 significant experience in both diseases. They, together with you and your parents, will be your own
652 care team.

653 As a result, it will be much easier for you to perform everyday activities. Your involvement will also
654 help us shape new standards of care for hundreds of other children with the same issues as you.

655 **Clinical trials and LAMAIinDiab study**

656 For over 75 years, doctors and scientists have tried to find an optimal approach to treat ADHD. New
657 drugs, investigated worldwide, give young people chances for better lives. Those studies are difficult
658 because they need young people like you to take some risk and trust in the proposed treatment plan.
659 New treatments often prove better than the previous ones, but not always. This is why clinical trials
660 are so important – they tell us what works best and how we can improve the treatment. Participants
661 in clinical trials, including children and adolescents, are treated following a detailed set of rules called
662 Study Protocol. Everyone, including the participants, must follow them for the trial to be adequate.
663 This also requires frequent check-ups to ensure the treatment is safe and efficient. In people with type
664 1 diabetes and ADHD, there have been no such studies yet, so we need to determine which treatment
665 can be best for you. That’s why we want you to take part in the LAMAIinDiab study. This study will test
666 the performance of two drugs – methylphenidate (MPH) and lisdexamfetamine (LDX). Both of these
667 drugs are known for their safety and effectiveness in ADHD treatment – however, we don’t know yet
668 which one will be better for you and how well they will improve your diabetes control. In this study,
669 you will undergo treatment with both drugs, one at a time. This will allow you to decide which of those
670 works best for you!

671 Experts have designed the treatment plan for treating diabetes and ADHD. It is up to your
672 parents/guardians to agree to your participation in this clinical trial – but your decision is also very
673 important to us.

674 **What will this study include?**

675 If you and your parents/guardians decide to enter this study, the first step is to sign the informed
676 consent form. This document will be signed by your parents/guardians. Remember, that you should
677 go through all the details and come to an agreement together. After the form is signed, you will be
678 required to follow the physicians' recommendations and inform your parents/guardians and physicians
679 about all unsettling symptoms and changes in your health, even those such as cold, headache or
680 trouble sleeping. The treatment will continue at your usual diabetology clinic and at your house using
681 remote online visits. This way, you will remain in contact with our team without needing to travel far.

682 If you enter the LAMAIinDiab trial, you and your parents/guardians will be invited for the first visit to
683 your diabetes care center to undergo examination by your primary diabetologist. It will be similar to
684 your regular visits at the clinic – we will measure your body weight, height and blood pressure.
685 Afterwards we will focus on your glycemic control and how it can be improved. We will collect blood
686 drop for standard glycated hemoglobin measurement, which will require us to prick your finger, but
687 you are already familiar with this procedure.

688 Other things will also happen. First, your parents/guardian will receive a blood pressure monitor and
689 tablet with an internet connection for the time of your participation in the trial. Those devices will be
690 used while trying determine the best drug dose for you. They will also limit the number of visits to the
691 hospital because we will use the tablet to connect with you and your parents/guardians as an online
692 visit. We are also interested in how active you are and how much sleep you get. This is important
693 because ADHD and drugs may impact your energy levels and activity throughout the day. This is why
694 we want to know your daily activity before and during treatment with each medication. You will get a
695 watch with a built-in activity monitor on the first visit. While you wear it, the watch will collect data on
696 how active you are, if you are walking, running, or sleeping. We would like you to wear this watch three
697 times during this trial, each for two weeks. This will allow us to analyze the collected data and
698 determine the effect of treatment while you will not need to carry the watch all the time. At the end
699 of your participation in the trial, you will return all the borrowed devices: blood pressure monitor,

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3 700 tablet, and watch with built-in activity monitor. This will allow us to download all the clinical data from
4 701 those devices and prepare them for the next study participant. So please, take care of those devices.

6 702 We would like you to use continuous glucose monitoring (CGM) sensors during the trial. Those small
7 703 devices, similar to insulin pump infusion sets, are put on the skin. With the tiny needle, they allow for
8 704 continuous glucose level measurement which can be accessed by a mobile device or insulin pump.
9 705 Maybe you already use CGM, and it is part of your everyday life. If that is so, participation in the study
10 706 will not require any changes. If you are not using CGM now (never used it or used it in the past), we
11 707 would like you to use one during the LAMaInDiab study. We believe using CGM will help you control
12 708 your diabetes better, reducing the need for fingerpricks. If you decide to use CGM, your physician will
13 709 provide you with the appropriate sensors and instruct you on how to use them properly. However, if
14 710 you don't want to use CGM, they are not mandatory in this trial, even though we highly recommend
15 711 you give it a try!

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19 712 In addition to the visit in diabetes care centre, we will invite you for the online visit with one of the
20 713 study investigators. During the visit, you will answer some questions on how much ADHD affects your
21 714 daily life now – and will allow us to measure how much this will improve throughout the trial. Some of
22 715 the questions you may find tedious or tiring, but they are essential! How you answer them is critical
23 716 for us to understand your experiences and determine which treatment is better for you and others.
24 717 With your parents, you will answer those questions multiple times throughout the study, so please
25 718 answer as sincerely as possible. This will make it easier for us to notice any meaningful changes.

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28 719 At the end of the trial entry visits, we will try and help you control ADHD and type 1 diabetes, just as
29 720 we promised. To do it, we will use two essential methods: (1) parental education and „training” and
30 721 (2) pharmacotherapy. Moreover, if you are a girl, your primary physician will discuss pregnancy
31 722 prevention, which will be required during your participation in the study.

33 723 **Part I: Parental education and „training”**

35 724 During the first three months (10-12 weeks) of your participation in the study, your parents/guardians
36 725 will participate in 10 weekly online training sessions in small groups with an education expert. During
37 726 the sessions, the expert will teach your parents what ADHD is, how to manage its symptoms and help
38 727 you control it. Each session will last 90 minutes and will cover training and discussion of one topic. You
39 728 may think about this parental education as if they got back to school because, similarly to you, they
40 729 will get some „homework” to do between classes. After the training, your parents will learn how to
41 730 control best and manage difficult situations of ADHD aggravations. Some of those methods are useful
42 731 in other cases and will hopefully foster a more active approach to support and care for your parents.
43 732 Parental training will include scenarios and educational materials to expand your parents' knowledge
44 733 of ADHD and your struggles. For the training to be completed, at least one of your parents must
45 734 participate in 8 out of 10 meetings. If this is not possible during one series of sessions, there is an
46 735 opportunity to participate in the remaining meeting in the next series. However, if your parents do not
47 736 participate in the training, we will not be able to continue your participation in the second part of the
48 737 trial.

53 738 **Part II: Pharmacotherapy**

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55 739 After your parents finish their education sessions, we will check again if ADHD treatment is still
56 740 necessary for you – maybe you and your parents working together is enough for you to control your
57 741 ADHD. To make sure, we will again ask you and your parents/guardians for an online visit with our
58 742 investigator, who will ask you the same questions as at the start of the study. Based on your and your
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3 743 parents'/guardians' answers, the investigator will decide if ADHD still significantly affects your activity
4 744 and attention – and if you are eligible for pharmacotherapy.

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6 745 Before giving you any medication, we must ensure the drugs are adequate for you. Some medicines
7 746 cannot be taken if there are other preexisting conditions. We will carefully evaluate your health status
8 747 during a visit in diabetology clinic. This visit may take significantly longer than usual – you may need to
9 748 spend up to a few hours with us. Outside standard weight and height measurement, glycated
10 749 hemoglobin and diabetologist consultation, we will assess if you have any contraindications for the
11 750 treatment. We will measure your blood pressure, consult you with the ophthalmologist and record
12 751 your heart rhythm with ECG. We will also collect a sample of your blood for laboratory tests.

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15 752 And at last, we will also need a sample of your urine – which will be checked for any other drugs that
16 753 could interact with the study drugs. The urine sample will also be used for a pregnancy test if you are
17 754 female. Don't worry too much about it. All those tests are routinely required in clinical trials, and we
18 755 want to be sure that we know about all possible things that could affect how pharmacotherapy
19 756 interacts with other substances in your blood. If the drug test gives a positive result or your
20 757 parents/guardians report your use of illicit substances – we will stop your participation in the study.

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23 758 After we are sure to proceed, we will ask you and your parents/guardians to participate again in an
24 759 online visit with the physician, who will talk to you and then enroll you for the first treatment. The
25 760 drug you will start with will be picked randomly – think about it as if it was a coin toss – heads is drug
26 761 A, tails – is drug B. Such choosing method is standard in clinical trials and lets us be sure that observed
27 762 effects really come from the used drug. Also, do not worry. the second drug will still be provided for
28 763 you after we evaluate the effects of the first one.

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31 764 After the drug selection, your physician will instruct you and your parents/guardians about the
32 765 treatment procedure, how much and how often you should take the drug, and how to administer it.
33 766 Please, remember, together with your parents/guardians, to take medicine systematically. If taken as
34 767 advised by the physician, it will improve your control of ADHD and allow us to evaluate its
35 768 effectiveness. The physician will also let you know what adverse events you may expect and what you
36 769 should watch out for. Remember –adverse events may occur, but it does not mean they will necessarily
37 770 happen to you. This also does not mean that the drug will not work. Finally, the physician will decide
38 771 on a starting dose and write you a prescription, with which your parents can pick up the medications
39 772 at the hospital.

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43 773 Also, at the start of the treatment, we will ask for the severity of ADHD symptoms and your appetite.
44 774 Those questions will be repeated during next online visits (after 1, 3, and 5 weeks respectively), as your
45 775 physician will adjust the medication dose appropriately. This will provide you with the optimal drug
46 776 dose that helps you control ADHD with the lowest risk of adverse events. During the dose adjustment
47 777 period, we will ask you to carefully observe your well-being and measure your blood pressure using
48 778 the provided blood pressure monitor every other day before 9 am and between 2 and 6 pm. You don't
49 779 need to note those measurements down; this device will remember them and send them to your
50 780 physician. During the online visits, the physician will again ask questions regarding ADHD severity and
51 781 appetite and evaluate the blood pressure measurements. You will also be asked if any adverse events
52 782 occurred and how frequently – so please note them as they happen. After the physician goes through
53 783 all the details and collected information, they will decide if and how to adjust the dose and provide
54 784 your parents/guardians with the appropriate prescription. We hope we can shoes the best dose within
55 785 five weeks. However, if it proves difficult, we will plan another visit after seven weeks for the final dose
56 786 adjustment and check-up. As the treatment dose is determined for you, things will slow down a bit –

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3 787 your parents/guardians will get the prescription for your medication for the next few weeks, and you
4 788 will no longer have to measure your blood pressure so often – now, only once per week will suffice.

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6 789 After three months of treatment, we will invite you for a visit to your diabetology clinic. During this
7 790 visit, the standard diabetology consultation will ensue, with height, weight and glycated hemoglobin
8 791 measurement, and CGM evaluation if you decide to use the sensor. Additionally, we will collect four
9 792 blood drops on a special paper strip, which will be sent to the laboratory, where our laboratory experts
10 793 will measure how much of the drug is in your bloodstream. This is important because it will tell us if
11 794 you did not forget about your daily dose and if the drug is absorbed and processed in your body
12 795 correctly. We will also instruct you how to collect your blood on such a special paper strip, as we would
13 796 like you to do so again before your next visit to the clinic. Your parents/guardians will be informed by
14 797 text message on the day of sample collection. Don't worry. This will be similar to blood collection for
15 798 self-monitoring blood glucose using your standard glucometer!

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19 799 During this visit we can also slightly modify the dose of your medication if you or your
20 800 parents/guardians want that. However, if the needed adjustment is considerable or if your diabetes
21 801 care physician sees it necessary, this will require an additional online visit.

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23 802 After that visit, you will continue the treatment and measure your blood pressure once every week.
24 803 After the end of the first treatment (6 months after the start), we will ask you the standard questions
25 804 regarding ADHD severity during another online visit. Comparing your responses before and after six
26 805 months of treatment will allow us to determine how effective the treatment was. Next, you will revisit
27 806 your diabetology clinic. All the standard visit procedures will be repeated (height, weight, blood
28 807 pressure, HbA1c measurement, CGM evaluation), including the above-mentioned dried blood spot
29 808 collection. However, this visit again will be a longer one. Once again, we will perform an ophthalmology
30 809 consultation and heart rhythm recording (ECG), and a blood sample will be collected for additional
31 810 tests. This is required, so we are sure you are eligible for the second drug treatment. Before we start
32 811 the subsequent treatment, we must be sure that the first drug is no longer in your organism – this
33 812 requires a 3 to 7 days „wash-out“ period. The online visit will initiate the second drug treatment, as
34 813 was the case for the first drug. We will again ask questions regarding ADHD severity and begin the dose
35 814 adjustment, following the same online visit plan as for the first treatment. Diabetology visits will ensue
36 815 at 3 and 6 months, as for the first treatment. The last diabetology visit (after six months of the second
37 816 treatment) will be your last study visit, during which we will ask you to bring all the borrowed devices
38 817 and discuss your experiences in the trial.

39 818 **Procedures of the study and associated inconveniences**

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45 819 To properly perform this study, we will need your cooperation. During the trial, you will often
46 820 participate in additional visits, examinations or tests – simply, procedures. Some may seem tedious or
47 821 time-consuming, and others you might not like – but thanks to you and your cooperation, we hope to
48 822 make them as effortless as possible. Below, you can find a detailed description of each procedure,
49 823 along with information on potential risks and associated inconveniences. If you or your
50 824 parents/guardians have additional questions regarding the procedures, we are ready to provide
51 825 detailed answers! Don't be afraid to ask your physician questions regarding the procedures if anything
52 826 makes you curious or worried!

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55 827 **1) Medical history and physical examination.** During each visits, you will be carefully
56 828 examined by each Investigator. Do not worry – this will be a normal visit to the doctor
57 829 and will resemble routine physician visits. Each investigator will ask you how you feel
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3 830 (history taking), and while the diabetologist will examine you physically. These
4 831 procedures carry no additional risk or discomfort.
- 5 832 **2) Glycated hemoglobin measurement from capillary blood.** Every three months, during
6 833 diabetology visits, we will ask you to provide a capillary blood sample. This will be
7 834 performed by a simple fingerprick that you have previously experienced many times
8 835 during self-monitoring of blood glucose using a standard glucometer. This is a common
9 836 procedure during diabetology visits, and although it may hurt a bit, it won't be more
10 837 than you are used to.
- 11 838 **3) Capillary blood collection on the special paper strip – drug concentration**
12 839 **measurement from the dry blood sample.** We will ask you three times during the
13 840 study to provide a capillary blood sample (4 drops) on the special paper strip. This is
14 841 required, as we will measure the drug concentration from this sample to ensure you
15 842 are taking your medication and if its levels are not affected by biological processes in
16 843 your body. The sample collection resembles the collection of glycated hemoglobin or
17 844 self-monitoring of blood glucose. It won't hurt more than those abovementioned
18 845 procedures you are already used to.
- 19 846 **4) Urine sample tests (pregnancy and drugs test).** For you to be eligible for the
20 847 pharmacotherapy, we need to perform a few studies from the urine sample. We will
21 848 ask you to provide a sample in the special container on the day of the diabetology visit.
- 22 849 **5) Blood pressure and heart rate measurement.** During the diabetology visits, we will
23 850 measure your blood pressure using an automated blood pressure monitor – 3 times
24 851 on each arm. Additionally, you will be provided a blood pressure monitor for your
25 852 participation in the study, so you can measure your blood pressure when you are under
26 853 treatment. This procedure may be bothersome because it requires proper preparation
27 854 (you must sit down, rest and relax for a few minutes before the measurements), but
28 855 we hope you will manage to do it!
- 29 856 **6) Anthropometric measurements.** During the control visits at the diabetology clinic, we
30 857 will perform standard height and weight measurements using proper measurement
31 858 devices. The measures will be carried out by trained hospital personnel.
- 32 859 **7) Physical activity and sleep monitoring with wristwatch with built-in activity monitor.**
33 860 We will collect your data on physical activity and sleep quality during the study using a
34 861 wrist activity monitor. Those measurements are not invasive and will only last for the
35 862 last two weeks of parental training and during the pharmacotherapy. We ask you to
36 863 wear the wristwatch with a built-in activity monitor on the wrist of your non-dominant
37 864 for two weeks for 24 hours (including while you are asleep). Although it may be
38 865 bothersome at the start, those watches were designed to be worn all day, and you will
39 866 quickly get used to wearing them. If you want, you may continue to use the watch
40 867 throughout the whole study period.
- 41 868 **8) Heart rhythm recording with ECG.** During the examination prior to the
42 869 pharmacotherapy, we need to record your heart rhythm – this will be performed twice
43 870 using a standard ECG device. This procedure is not invasive and takes only a minute.
- 44 871 **9) Ophthalmologist consultation.** During the examination before the pharmacotherapy,
45 872 we need to measure your intraocular pressure and perform gonioscopy. Those are two
46 873 routine ophthalmological procedures, and both are non-invasive. However, you may

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3 874 find those measurements not comfortable. They will be performed only twice, and
4 875 despite mild discomfort, they are quickly performed and should not cause any pain.

6 876 During the study, we will also use three questionnaire tools – Conners 3 (parent and child versions),
7 877 PedsQL QoL and Diab (parent and child versions), appetite questionnaire and ADHD symptoms severity
8 878 (Likert-scale based tests). As we already described, we will often ask you questions from those
9 879 questionnaires. But it is required, as this will allow us to understand better how you manage your
10 880 ADHD and type 1 diabetes and if the treatments are effective. Thanks to your answers, we can provide
11 881 you with the optimal drug dose and minimize the risk of adverse events and associated discomfort.
12 882 Although the visits may differ, those questions will always be asked. The questions will be asked by
13 883 trained personnel with extensive experience in collecting answers and evaluating questionnaires.
14 884 Please don't hesitate to ask them any questions!

17 885 **General information**

18 886 Your opinion is critical in the final decision on your participation in LAMAinDiab. However, you must
19 887 know that the final decision is made by your parents/guardians. Suppose you and your
20 888 parents/guardians will not agree for your participation in the study, or decide to refuse your further
21 889 participation at any moment. In that case, you will be treated following the best current standards.
22 890 Outside of this study, type 1 diabetes may be treated by a diabetologist, while a psychiatrist may help
23 891 with optimal ADHD treatment.

24 892 For LAMAinDiab to be possible, it is required for many hospitals and institutions to cooperate closely.
25 893 As such, some information regarding you (such as name, surname, and date of birth) and your medical
26 894 and treatment history may be transferred between those institutions. Moreover, this data may be
27 895 provided to regulatory agencies under some circumstances. Remember that all the people involved in
28 896 this study, and those in regulatory agencies, who at any point have access to your data, must keep this
29 897 data safe, protected, and held a secret.

30 898 **Sample storage (biobanking) and auxiliary studies**

31 899 Samples collected during this study, such as your blood, serum, and special paper strips, will be marked
32 900 with your identifying number and kept at the Medical University of Lodz for five years after the study
33 901 completion. The information on the storage is accessible to you and your parents/guardians. Auxiliary
34 902 studies that may help better understand the disease and treatment mechanism may be conducted in
35 903 the future.

36 904 **Contact us**

37 905 If you have any more questions regarding ADHD and type 1 diabetes treatment or the LAMAinDiab
38 906 study, feel free to discuss it with your parents/guardians or your physician at your convenience.

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Information for the Patient (13-18 years old)

For peer review only

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3 922 **Information for the Patient (13-18 years old)**
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5 923 LAMAIinDiab - lisdexamfetamine vs methylphenidate for pediatric patients with ADHD and type 1
6 924 diabetes - a randomized crossover clinical trial
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10 926 **Study sponsor: Medical University of Lodz**

11 927 **Primary researcher:**

12 928 **Research facility (full name, address, telephone):**

13 929 **Researcher:**

14 930 **Researcher's phone number:**

15 931 Patient number: _____
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23 933 **Hi!**

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25 934 We are a group of doctors and scientists who work together to help people with diabetes cope with
26 935 the disease and enjoy life - you have already met some of us in your Diabetes Clinic. We come to you
27 936 because we know that in addition to type 1 diabetes, you also have an additional problem, which is
28 937 ADHD. We believe that the right treatment for ADHD can help you feel better – and keep your diabetes
29 938 under control. That is why we invite you to participate in the LAMAIinDiab study.

30
31 939 First, we'll show you what ADHD is and how it relates to diabetes. Then we will tell you how we would
32 940 like to help you. The information you are reading now consists of several pages of text. Therefore,
33 941 please - ask about things that interest you or that you do not understand, we will try to answer as best
34 942 we can and explain what is unclear. You can write down your questions and ask your doctor after
35 943 reading the Information form.
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38 944 **What is ADHD?**

39
40 945 ADHD, or Attention Deficit Hyperactivity Disorder, is a disorder that affects every twentieth person -
41 946 so it is more common than diabetes! People with ADHD find it hard to sit still and focus e.g. at school
42 947 during a lesson or while doing homework. Have you ever forgotten to measure your blood sugar or
43 948 made a mistake when counting your insulin? Forgot a meal? This can be caused by this disease and not
44 949 your fault. In our study, we want to help you deal with problems related to ADHD and type 1 diabetes.
45 950 As part of the LAMAIinDiab study, we will create conditions for you that will make it easier for you to
46 951 control diabetes and ADHD.
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49 952 **How do we treat ADHD?**

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51 953 There are two main strategies to treat ADHD. The first of them is teaching you and your parents on
52 954 how to effectively deal with problematic behaviors. The second, essential element is taking
53 955 medications that help to "calm the storm" in your head and focus on the things you want to achieve.
54 956 Unfortunately, combining these drugs with diabetes therapy is difficult, and few physicians are able to
55 957 reconcile the two therapies.
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58 958 The LAMAIinDiab study is designed to provide you with the care of these experts who know both
59 959 diseases very well. You will be under the care of a well-coordinated team, of which you will also be a
60 960 part as a patient. This will ensure the highest quality of care for you, and it will allow us to create

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3 961 standards thanks to which hundreds of other children and young people with similar problems will also
4 962 be able to benefit from such care in the future!

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6 963 **Clinical trials and the LAMAIInDiab study**
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8 964 Research into the optimal treatment of ADHD has been ongoing for 75 years. New drugs, tested all
9 965 over the world, give young people hope for better functioning. These studies are difficult to conduct
10 966 because they require young people like you to take some risks and trust in the treatment plan prepared
11 967 by the research team. Often the new treatment turns out to be better than the old one - but not
12 968 always. It is clinical trials like this that tell us what works well - and what needs to be improved. People
13 969 participating in clinical trials, including children and adolescents, are treated according to specific rules,
14 970 the so-called Research Protocol that they must follow. In addition, they are closely monitored to ensure
15 971 that the treatment is safe and effective.

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18 972 For people with type 1 diabetes and ADHD, there are no such studies yet - so we don't know what
19 973 treatment might be best for you. That is why we want to ask you for your help and participation in the
20 974 LAMAIInDiab study. In total, we intend to ask 150 patients to take part. During the study, we would
21 975 like to test the effects of two drugs - methylphenidate (MPH) and lisdexamfetamine (LDX). Both are
22 976 known, good, safe, and effective drugs in the treatment of ADHD - but we don't know which one will
23 977 be better for you and how their use can help you treat diabetes. If you take part in the study, you'll
24 978 alternate between the two - and then you'll tell us which one makes you feel better. This is the first
25 979 study that will allow us to answer many questions, but above all, provide you and others struggling
26 980 with this problem with the best possible therapy!

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30 981 If your parents/legal guardians consent, you will have a chance to participate in this clinical trial.
31 982 However, your opinion is also very important and can influence the final decision!

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33 983 **How will the study be conducted?**
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35 984 If you and your parents/legal guardians decide to participate in the study, the first step will be to sign
36 985 a document called an informed consent form. This document is signed by you and your parents/legal
37 986 guardians. However, remember that you should discuss all issues together, and it should be your joint
38 987 decision. After agreeing to participate in the study, you will be obliged to follow the recommendations
39 988 of doctors and inform your parents/legal guardians and doctors about all disturbing symptoms and
40 989 deterioration of health observed, even such as colds, headaches, and sleep problems.

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43 990 Treatment in the study will take place in your current diabetes clinic - and in your home, using online
44 991 consultations. This way, you will be in constant contact with us and you will not have to travel far.

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46 992 If you start participating in the LAMAIInDiab study, you will receive an invitation for you and your
47 993 parents/legal guardians to a diabetes appointment, during which you will be thoroughly examined by
48 994 your doctor. During the visit, we will measure your weight, height, and blood pressure. In addition, the
49 995 doctor will analyze your diabetes control and advise you on how to manage it better. We will also take
50 996 a drop of blood from your finger for a glycated hemoglobin test - as you well know, this involves a slight
51 997 prick in the finger to which you are accustomed. However, since this will be a clinical trial visit, we have
52 998 prepared a few extra things that will happen.

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55 999 First of all, your parents/legal guardians will receive from us a blood pressure measuring device and a
56 1000 tablet with internet access as part of the clinical trial. These devices will be necessary to properly adjust
57 1001 the dose of the drug so that it meets your needs. This will also allow us to reduce the number of
58 1002 burdensome hospital appointments and provide you with the highest quality of treatment.
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3 1003 We are also interested in how active you are and whether you sleep well - this is very important
4 1004 because both ADHD and the study drugs can affect your energy and activity levels during the day. We
5 1005 will analyze what your daily activity looks like before the study drugs are administered, and how it is
6 1006 affected by the investigated drugs. For this purpose, during your first appointment, you will receive a
7 1007 wrist watch that will measure this activity. It will do this by registering your hand movements when
8 1008 you are sitting, walking, running, or sleeping. During the study, we will ask you to wear the watch three
9 1009 times for two weeks - so that we can collect the necessary data and not burden you with another
10 1010 device. We will also ask you to keep your watch on at night as we want to assess how your treatment
11 1011 affects the length and quality of your sleep.

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14 1012 At the end of the study, the watch, tablet, and blood pressure monitor will be returned to the hospital
15 1013 so that we can accurately assess your progress in the study, and the equipment will be passed on to
16 1014 subsequent young patients who also participate in the study. That's why we ask you - take care of the
17 1015 equipment you will get together with your parents!

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20 1016 During your participation in the study, we would like you to use continuous glucose monitoring (CGM).
21 1017 It is a small device resembling an insulin pump infusion set, inserted subcutaneously. It continuously
22 1018 tracks your blood, which you can read on your phone or insulin pump. If you use CGM on a daily basis,
23 1019 participation in the study does not change anything for you, and during subsequent appointments, we
24 1020 will use the data collected by the system to assess the control of your diabetes. If you have not used
25 1021 CGM before or are not currently using it - we would like to offer you the opportunity to use it while
26 1022 participating in the study. We believe that this will make it easier for you to control your diabetes and
27 1023 will allow you to measure your blood glucose level less often with a glucometer. If you decide to use
28 1024 CGM, your doctor will give you the sensors and tell you how to use them properly. The use of CGM is
29 1025 not mandatory to participate in the study, but we sincerely recommend that you at least try!

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33 1026 In addition to the diabetes appointment, we will also invite you to a teleconsultation with the
34 1027 investigator at the beginning of the study. They will ask you a series of questions to assess how much
35 1028 of a problem ADHD is for you - and then to measure improvement. The entire examination will take
36 1029 about 30-40 minutes. This study and all the questions asked during it will be repeated in subsequent
37 1030 teleconsultations of this kind - and are extremely important for the success of the study. Therefore,
38 1031 we ask for your patience and understanding. We do this to reliably assess the change in the severity of
39 1032 your ADHD symptoms and your quality of life at the beginning of the study and in the subsequent
40 1033 stages of treatment - which will allow us to compare the effectiveness of the interventions and
41 1034 medications used.

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44 1035 After these initial appointments, we will try to help you manage your ADHD and type 1 diabetes as
45 1036 promised. We want to do this in two ways – each of which is part of our study.

- 46
47 1037 1. Education and parental "training".
48 1038 2. Administration of drugs

49 1039 If you are a patient who can become pregnant and have started engaging in sexual activities, you will
50 1040 also be asked to use effective contraception, and if you are not sexually active, the doctor will ask you
51 1041 to remain abstinent throughout the study.

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54 1042 **Part I: Parental education and training.**

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56 1043 During the first 3 months (10-12 weeks) of your participation in the study, your parents/legal guardians
57 1044 will participate in a series of 10 weekly online meetings in small groups with other parents of children
58 1045 with ADHD and an expert educator. During these meetings, an expert will explain to your parents what
59 1046 ADHD is, how to deal with its symptoms, and how to help you with it. Each of the 10 meetings lasts 90

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3 1047 minutes, during which one topic will be discussed in detail and worked through. You can think of these
4 1048 meetings as your parents' return to school as they will be given 'homework' from us to do between
5 1049 classes. After completing the training, your parents will learn methods that will make it easier for you
6 1050 all to control and cope with the events when ADHD symptoms get intense. This method is also effective
7 1051 in many other disorders. The training will also encourage and strengthen your parents' active attitude,
8 1052 focused on acquiring new knowledge and supporting you in new social situations. Parent training will
9 1053 take the form of structured group work with a prepared scenario and educational materials. These
10 1054 workshops are a method of expanding your parents' knowledge about your functioning and your
11 1055 relationship.

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14 1056 At least one of your parents/legal guardians must be present for 8 out of 10 meetings. If they cannot
15 1057 participate, they can retake up to 2 meetings during the next training cycle. The lack of participation
16 1058 of your parents/legal guardians in Part I of the study will unfortunately prevent you from further
17 1059 participating in the study.

20 1060 **Part II: pharmacotherapy**

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22 1061 After your parents/guardians finish the educational meetings, we will see if you need ADHD medication
23 1062 at all - maybe working through appropriate behaviors with your parents is enough to make you feel
24 1063 good. To assess this, we will again invite you and your parents/guardians to a teleconsultation with the
25 1064 investigator who will ask you the same questions as at the beginning of the study. If, based on your or
26 1065 your parents' answers, we see that ADHD still significantly affects your activity and attention - you will
27 1066 receive medication as part of a clinical trial.

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30 1067 First, we will make sure that the medicines we want you to take are suitable for you. We will determine
31 1068 all this during the appointment in diabetes clinic. This appointment will be longer than usual - you will
32 1069 spend a few hours in your center. During them, there will be standard tests and measurements that
33 1070 you know: height, weight, glycated hemoglobin from capillary blood, and diabetes consultation with
34 1071 CGM analysis. In addition, we will check whether you have any contraindications to start a new drug.
35 1072 For this purpose, we will measure your blood pressure, conduct an ophthalmological examination and
36 1073 record your heart (ECG). We will also take your blood for laboratory tests, the results of which will be
37 1074 assessed by your doctor before starting treatment. Finally, we will ask you for a urine sample - we will
38 1075 test it for the presence of drugs. Don't stress about it, this is standard in clinical trials, we want to make
39 1076 sure that the drugs given will not mix with other substances that affect the nervous system. If your
40 1077 urine test is positive for substances other than the study drugs, your doctor will terminate your
41 1078 participation in the study. This will also happen if your parents/legal guardians confirm your use of
42 1079 illicit substances. In the case of girls, we will also perform a urine pregnancy test, as pregnancy is a
43 1080 contraindication to the study drug in the clinical trial.

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47 1081 After visiting the center, we will invite you for teleconsultations with a doctor who will decide on your
48 1082 treatment. They will do it based on the results of your tests and the medical interview. The drug you
49 1083 receive at the beginning will be chosen randomly - think of it as a roll of the dice (even result - drug A,
50 1084 odd result - drug B). This choice of treatment is at the heart of clinical trials and ensures that the effects
51 1085 of treatment really depend on the drug you receive. Also, don't worry, in this study you will have the
52 1086 option to try both drugs, we only draw their order.

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55 1087 After selecting the drug, the doctor will tell you and your parents/legal guardians about its effects,
56 1088 determine how much and when you should take it, and answer your questions. Please try to remember
57 1089 with your parents/legal guardians about taking the medicine regularly, as it will help you feel better
58 1090 on a daily basis and help us to evaluate its effectiveness. The doctor will also tell you what the side
59 1091 effects of the medicine may be and what to look for when taking it. Remember – the fact that side

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3 1092 effects may occur does not mean that they will happen to you, nor will they make the medicine
4 1093 ineffective. The doctor will issue a prescription that will allow your parents/legal guardians to collect
5 1094 the medicines at the Hospital. He will also ask you and your parents/guardians to specify how
6 1095 troublesome your ADHD symptoms are for you and what your appetite is - these questions will be
7 1096 repeated at subsequent visits and will help choose the right dose of medicine for you.

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10 1097 The dose of medicine needed is a little different for each patient, so we will be checking in on how you
11 1098 are feeling often! We will assign you the next teleconsultation after 1, 3, and 5 weeks of taking the
12 1099 drug and we will ask you to closely monitor your well-being during this time. We will also ask you to
13 1100 regularly measure your blood pressure with a rented device - every other day, twice: before 9:00 and
14 1101 between 14 and 18:00. You do not have to save the measurements anywhere - the device will
15 1102 remember them and send them to your doctor. During these teleconsultations, we will talk about how
16 1103 you assess the intensity of ADHD symptoms and appetite over the last 7 days. The doctor will analyze
17 1104 the results of your blood pressure measurements and ask questions about the most common side
18 1105 effects of the drug. The doctor will then decide whether to keep or change the dose of your medicine
19 1106 - and will give your parents/legal guardians a prescription for the medicine. We hope that during these
20 1107 5 weeks, you will be able to find the best dose of the drug for you. If not, we will arrange an additional
21 1108 appointment for you and your parents/guardians after 7 weeks.

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25 1109 After setting the dose of the drug, things will slow down. You will receive a prescription for the drug
26 1110 for the next few weeks, and we will reduce the frequency of blood pressure checks (we will only ask
27 1111 you to check your blood pressure once a week).

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29 1112 After three months from the start of pharmacological treatment, you will be invited to an out-patient
30 1113 appointment in the clinic to undergo standard diabetes consultation. We will measure your weight and
31 1114 height, blood pressure, and heart rate, as well as assess diabetes control (by measuring HbA1c from a
32 1115 finger and downloading data from the CGM sensor). If you or your parents/guardians express such
33 1116 need, we may also reduce the dose of your medication during this appointment. If major changes are
34 1117 necessary or your diabetes doctor asks for it, then we can arrange an additional online visit with the
35 1118 Investigator who started your treatment with the study drug. In addition to drawing blood from your
36 1119 finger for HbA1c measurement, we will collect four drops of your blood on a special paper that we will
37 1120 send to the laboratory to check whether you took medications that day and how quickly your body
38 1121 processes them. We will also show you how to draw blood on this paper yourself because we would
39 1122 like you to do it again at home before your next visit. Don't worry, it's really easy - especially for you
40 1123 since you already know the glucose meter! The day when we ask you to draw blood will be determined
41 1124 by your doctor - we will send this information to your parents via text message.

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45 1125 After this appointment, you will continue your treatment for the next 3 months and measure your
46 1126 blood pressure once a week. At the end of this period (6 months from the start of treatment with the
47 1127 first drug) we will invite you to another assessment in the form of a teleconsultation, during which we
48 1128 will again ask you questions about your ADHD symptoms. Comparing your answers with those from
49 1129 earlier will allow us to assess how this drug affects your ADHD symptoms and your quality of life. After
50 1130 that, you will attend a diabetes appointment. During it, we will repeat the usual measurements (height,
51 1131 weight, blood pressure), take another blood sample on paper and assess the control of your diabetes
52 1132 (HbA1c measurement, CGM analysis). In addition, we will repeat the ophthalmological examination,
53 1133 ECG and take blood and urine samples - the results of these tests will later allow us to give you the
54 1134 second of the tested drugs. After this appointment, a short period will begin where you will be left
55 1135 without treatment. This will allow us to make sure that nothing of the study drug remains in your
56 1136 system when you start treatment with the other drug. Don't worry, this time it will be very short - 3 to
57 1137 7 days. It will end with another teleconsultation with the doctor who started your treatment with the

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3 1138 first drug. During it, we will repeat the same steps as during the appointment starting treatment. The
4 1139 only difference is that this time we will not draw a drug for you - you will just get a second drug that
5 1140 you have not used yet. Thus, you will start the second, 6-month treatment period in the clinical trial.
6 1141 It will consist of the same stages and appointments as for the first drug - teleconsultations after 1, 3, 5
7 1142 (possibly 7) weeks to select the dose, tele-assessment of ADHD symptoms, and stationary diabetes
8 1143 consultation after 3 and 6 months of treatment. The last diabetes consultation during this period will
9 1144 also be the last on-site visit in the study. During this final appointment, we will pick up the loaned
10 1145 equipment from you and your parents, and we will ask how you enjoyed participating in the study.

11 1146 **Examinations performed during a clinical trial and the inconveniences that may accompany them**

12 1147 In order to make the study successful, we need your cooperation. You will participate in additional
13 1148 meetings, tests, and activities (generally: procedures). Some of them may be boring or time-
14 1149 consuming, and others you may not like - but with your help and cooperation, we hope to get through
15 1150 them quickly. Below is a detailed description of each of the procedures, along with information on the
16 1151 inconvenience that may accompany them. If you or your parents/legal guardians have additional
17 1152 questions about the procedures, we are ready to provide comprehensive answers! Don't be afraid to
18 1153 ask your doctor-investigator about anything that interests or worries you!

- 19 1154 1. Examination. During each of your clinical trial appointments, we will conduct a full medical
20 1155 examination - this will be a normal appointment with your doctor, just like any other. The doctor
21 1156 examining you will always ask how you feel and if anything is wrong with you (subjective
22 1157 examination), and the diabetologist will additionally examine you physically (auscultate, examine
23 1158 your stomach, throat, etc.). All those procedures are non-invasive.
- 24 1159 2. Capillary blood sampling and measurement of glycated hemoglobin HbA1c. Every 3 months during
25 1160 diabetes appointments, we will ask you to prick your finger and take a drop of blood from you. The
26 1161 prick may hurt - but no more than checking your blood glucose daily with a blood glucose meter.
- 27 1162 3. Collecting a drop of capillary blood on a paper - measurement of drug concentration in a dry blood
28 1163 drop. Three times during the treatment, we will ask you to prick your finger and collect 4 drops of
29 1164 blood from you on a special paper. This paper will later go to the laboratory, where we will measure
30 1165 how much of the study drug was in your blood. The prick itself is similar to taking blood for glycated
31 1166 hemoglobin and will be done with a disposable needle.
- 32 1167 4. Urine tests (pregnancy test and drug test) – as part of a clinical trial, in order to qualify the patient
33 1168 for pharmacotherapy, it is necessary to perform urine tests. We will ask you to collect urine in a
34 1169 special container on the day of your diabetes appointment.
- 35 1170 5. Blood pressure and pulse measurement. During diabetes appointments, we will measure your
36 1171 blood pressure with an automatic blood pressure monitor - 3 times on the right and left arm. In
37 1172 addition, we will lend you a similar blood pressure monitor at home, which you will use to measure
38 1173 your blood pressure during your participation in the study. Prepare for each measurement (sit
39 1174 down, rest, and relax for a few minutes).
- 40 1175 6. Body measurements - as part of follow-up appointments at the Clinic, height, and weight
41 1176 measurements will be performed using appropriate measuring devices, performed by trained
42 1177 personnel.
- 43 1178 7. Measurement of activity and sleep quality using an accelerometer - as part of the clinical trial, data
44 1179 on physical activity and sleep quality will be collected using a wrist accelerometer (watch). These
45 1180 measurements are non-invasive and will continue for the last two weeks of psychotherapy and
46 1181 two 6-month pharmacotherapy cycles. The accelerometer will be worn by the study participant on
47 1182 the wrist of the non-dominant hand for 2 weeks around the clock (including the period of sleep).
48 1183 Patients will be allowed to use the accelerometer for the whole duration of the study at the
49 1184 reasonable request of a parent/legal guardian.

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3 1185 8. Electrocardiogram (ECG) - as part of recruitment for pharmacotherapy, two non-invasive
4 1186 recordings of the electromechanical work of the heart using ECG will be made in order to exclude
5 1187 functional disorders of the heart.
6 1188 9. Ophthalmological consultation – before starting pharmacotherapy, an ophthalmological
7 1189 consultation will be carried out with non-invasive measurement of intraocular pressure and
8 1190 assessment of the filtration angle in order to exclude glaucoma before initiating treatment.
9 1191 10. Questionnaires (Conners 3: Parent and Child, full version; PedsQL QoL and Diab, Parent, and Child,
10 1192 assessment of appetite and severity of ADHD symptoms - Likert scale). The questionnaires will
11 1193 allow us to check how you feel about ADHD symptoms and living with diabetes. Thanks to your
12 1194 answers, we will be able to choose the best dose of the drug for you - and also assess how effective
13 1195 it is. Questions will be asked by people trained for this purpose and analysis of your answers.
14 1196

17 1197 **General information**

19 1198 Your opinion will be crucial in deciding whether you will take part in the LAMAIInDiab study. If you and
20 1199 your parents do not consent to your participation in the study or withdraw it during the course of the
21 1200 study, you will be treated according to the best treatment available outside the clinical trial. If a patient
22 1201 is not participating in the LAMAIInDiab trial, they will be treated according to current standards by a
23 1202 diabetes physician and will be referred for treatment of ADHD by a physician specialist in this field.

26 1203 A study as large as the LAMAIInDiab study is only possible if many hospitals and other institutions, such
27 1204 as laboratories, work together. Therefore, some information about you (such as your name and date
28 1205 of birth) and about your illness and treatment will be exchanged between these places. It may also be
29 1206 necessary to share information with the specialists who are supervising this study. Remember,
30 1207 however, that all persons who obtain information about you and your illness are obliged to maintain
31 1208 full confidentiality.

34 1209 In addition, if the Research Team obtains new information about the clinical trial that may affect your
35 1210 further participation in the study, you and your parents/legal guardians will be immediately informed
36 1211 by the doctors from your facility. Your participation in the study is completely free. Neither you nor
37 1212 your parents/legal guardians will receive any financial compensation for your participation in the
38 1213 study.

40 1214 **Sample storage (biobanking) and additional tests**

42 1215 Samples collected during treatment, such as blood, blood serum, and test strips from a dry blood
43 1216 spot, will be marked only with the Patient's number (without identifying data), and then sent to the
44 1217 Medical University of Lodz, where they will be stored for a maximum of 5 years from the end of
45 1218 treatment. Information about the stored material will be available to you and your parents/legal
46 1219 guardians. Complementary research should help us better understand the causes of your condition
47 1220 and how your medications work and identify further risk factors. The aim is also to treat patients
48 1221 more effectively according to their individual regimens.

51 1222 **Please contact us if you have any further questions**

53 1223 If you have further questions about the disease or the LAMAIInDiab study, you can discuss them with
54 1224 your parents or doctor at any time, including now.

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3 1226 Informed consent form for participation in a clinical trial
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5 1227 **LAMAI nDiab – lisdexamfetamine vs methylphenidate for pediatric ADHD patients with type 1**
6 1228 **diabetes - randomized crossover clinical trial**
7

8 1229 Patient's name:
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- 10 1230 1. I confirm that I have read and understood the **Patient Information** regarding this clinical trial. I had
11 1231 the opportunity to read the information provided, ask questions, and receive satisfactory answers.
12 1232 2. I understand that my participation in the study is voluntary, and I can withdraw from it at any time
13 1233 without giving any reason, without affecting the medical care provided and my rights.
14 1234 3. I have been informed that the doctor conducting the study (Investigator) may decide to withdraw
15 1235 my participation in the study for medical reasons, as well as in the event of non-compliance with
16 1236 the recommendations
17 1237 4. I consent to the researcher's access to my medical records prior to the commencement of the
18 1238 clinical trial.
19 1239 5. I agree that after the end of the study, the information collected will be analyzed, presented at
20 1240 conferences, published in scientific journals, and used to develop new therapies.
21 1241 6. I understand that my biological samples will be analyzed for the purpose of this study.
22 1242 7. I have read and accept the general terms and conditions of third-party liability insurance of the
23 1243 Sponsor and the Investigator.
24 1244 8. I undertake to follow the recommendations regarding the clinical trial that will be provided to me
25 1245 by the Research Team.
26 1246 9. I have been informed that I will receive a copy of the Patients Information and a copy of the
27 1247 Informed Consent Form.
28 1248 10. I give my voluntary consent to participate in this clinical trial
29 1249 11. Consent to storage of biological material
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34 1251 You have the option of consenting to the Investigators using samples of biological material collected
35 1252 from your child for storage in research centers in Łódź, Gdańsk, Katowice, or Opole. Whatever you
36 1253 decide, it will not affect your medical care. You may continue to participate in the study even if you
37 1254 decline.
38

39
40 1255 After deciding, please mark the answer with a cross

41 1256 "YES" if you consent to the obtained biological material being stored and/or used to perform optional
42 1257 tests, or "NO" if you do not wish to keep any samples. YES NO
43
44

45 1258

46 **Name and surname of the Child** **Date** (handwritten) **Signature** (handwritten)
47 (Capital letters)

49 **Name and surname of the** **Date** (handwritten) **Signature** (handwritten)
50 **Investigator receiving the**
51 **Consent**

52 (Capital letters or stamp)
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3 1261 Consent form for the processing of personal data of a participant in the **LAMaInDiab clinical trial -**
4 1262 **lisdexamfetamine vs methylphenidate for pediatric patients with ADHD syndrome and type 1**
5 1263 **diabetes - randomized crossover clinical trial**

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7 1264

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9 1265 Patient's name:

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11 1266 I consent to the processing of my minor child's Personal Data in the scope of name and surname, date
12 1267 of birth, gender, PESEL number, and data from the shared medical documentation, for the purpose of
13 1268 conducting this clinical trial, as well as my Personal Data in the scope of name and surname for the
14 1269 purpose of proper processing and documenting the study. I declare that I have been informed about
15 1270 the purposes, scope, and conditions of processing Personal Data in accordance with art. 13 GDPR. I
16 1271 also declare that I have received a copy of the information clause, which is Appendix 1 to this form.

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Name and surname of the Parent/Legal Guardian (Capital letters)	Date (handwritten)	Signature (handwritten)
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Name and surname of the Parent/Legal Guardian (Capital letters)	Date (handwritten)	Signature (handwritten)
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3 1275 **Appendix 1**

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5 1276 Information clause regarding the processing of Personal Data for the purpose of conducting and
6 1277 controlling a clinical trial on "**LAMAIinDiab - lisdexamfetamine vs methylphenidate for pediatric**
7 1278 **patients with ADHD syndrome and type 1 diabetes - randomized crossover clinical trial**".

9 1279 According to Art. 13 sec. 1 of Regulation (EU) 2016/679 of the European Parliament and of the Council
10 1280 of 27 April 2016 on the protection of individuals with regard to the processing of Personal Data and on
11 1281 the free movement of such data, and repealing Directive 95/46/EC (General Data Protection
12 1282 Regulation) (hereinafter: "GDPR"), we inform you that:

- 13
14
15 1283 1. The administrator of the Personal Data provided by you for the purpose of conducting and
16 1284 controlling this clinical trial is the Medical University of Łódź, ul. Al.Kościuszki 4, 90-419 Łódź
17 1285 (hereinafter referred to as: "Sponsor"). These data include both the Patient's Personal Data,
18 1286 i.e. a minor on behalf of whom you gave consent to participate in the study, and your personal
19 1287 data as a legal guardian to the extent necessary for the processing and implementation of the
20 1288 study (hereinafter jointly referred to as: "Personal Data").
21 1289 2. Contact with the Administrator is possible via the e-mail address iod@umed.lodz.pl.
22 1290 Regardless of the possibility of contacting the Sponsor's Personal Data Protection Officer, any
23 1291 questions can be directed to the Investigator who is conducting the study.
24 1292 3. The Personal Data provided by you will be processed on the basis of art. 9 sec. 2 letter a) and
25 1293 j) of the GDPR in order to monitor the safety of pregnancy.
26 1294 4. All Personal Data provided by you will be pseudonymized (instead of the name and surname,
27 1295 the data will be marked with a code).
28 1296 5. The personal data provided by you will be made available to the Medical Research Agency
29 1297 with its registered office at ul. Stanisława Moniuszko 1A, 00-014 Warsaw, which is the entity
30 1298 financing the study. For the purpose of conducting the test, your personal data may be made
31 1299 available to the Research Center where the test is carried out, to an external monitor, as well
32 1300 as to external laboratories testing samples as part of the test.
33 1301 6. Access to the data provided by you may also be obtained by authorized persons and bodies,
34 1302 in particular the Bioethical Committee approving the Study, as well as the Sponsor's
35 1303 subcontractors (including external service providers, e.g. providers of technical, ICT services,
36 1304 diagnostic equipment, legal services, inspection services, etc.) or partners, persons involved in
37 1305 conducting the study, in particular, study observers (monitors), auditors, inspectors, doctors,
38 1306 nursing team, as well as national institutions supervising the study, provided that the received
39 1307 data is kept confidential.
40 1308 7. Based on the personal data provided by you, no decisions will be made in an automated
41 1309 manner and the data will not be subject to profiling.
42 1310 8. The personal data provided by you will not be transferred to a third country outside the
43 1311 territory of the European Union and the European Economic Area.
44 1312 9. The Personal Data provided by you for the purposes of monitoring the course of pregnancy
45 1313 safety will be processed for a period of 5 years, and medical documentation - if it was created
46 1314 - for a period of 20 years.
47 1315 10. You have the right to lodge a complaint to the President of the Office for Personal Data
48 1316 Protection for unlawful processing of Personal Data.
49 1317 11. You have the right to access the content of Personal Data and the right to rectify, delete, limit
50 1318 processing, the right to transfer data, the right to raise objections, the right to withdraw
51 1319 consent at any time without affecting the lawfulness of processing, which was made on the
52 1320 basis of consent before its withdrawal - within the limits specified in the law.
53 1321 12. Providing your Personal Data is fully voluntary and has no impact on the implementation of
54 1322 the Research
55 1323

1 Administrative information:

2 TRIAL REGISTRATION:

3 Date and trial version identifier: **LAMA/2021/1, Ver. 2.0.14.11.2022, 2022-11-14**

4 WHO Trial Registration Data Set (1.3.1):

- 5 • Primary Registry and Trial Identifying Number: **UR/DBL/D/263/2022 (The Office for**
- 6 **Registration of Medicinal Products, Medical Devices and Bioicidal Products/Urząd**
- 7 **Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych**
- 8 **– URPL)**
- 9 • Date of Registration in Primary Registry: **2022-11-14**
- 10 • Secondary Identifying Numbers: **2022-001906-24 (EUDRA-CT), NCT05957055**
- 11 **(ClinicalTrials.gov)**
- 12 • Source(s) of Monetary or Material Support: ***Competition for non-commercial clinical***
- 13 ***trials in the field of psychiatry and neurology (ABM/2021/2)*** from Medical
- 14 **Research Agency**
- 15 • Primary Sponsor: **Medical University of Lodz**
- 16 • Secondary Sponsor(s): **Not applicable**
- 17 • Contact for Public Queries: **Medical University of Lodz, Kościuszki 4, 90-419 Łódź,**
- 18 **422725239, lamaindiab@office365.umed.pl**
- 19 • Contract for Scientific Queries: **Agnieszka Butwicka, PhD, MD, Mazowiecka 15, 92-**
- 20 **215 Łódź, +48660445966, agnieszka.butwicka@umed.lodz.pl**
- 21 • Public Title: ***LAMAI nDiab - lisdexamphetamine vs methylphenidate for pediatric***
- 22 ***patients with ADHD and type 1 diabetes - a randomized cross-over clinical trial***
- 23 • Scientific Title: ***LAMAI nDiab - lisdexamphetamine vs methylphenidate for pediatric***
- 24 ***patients with ADHD and type 1 diabetes - a randomized cross-over clinical trial***
- 25 • Countries of Recruitment: **Poland**
- 26 • Health Condition(s) and Problem(s) Studied: **Patients with ADHD (MedDRA 23.0 LLT**
- 27 **10068453, SOC 100000004873) and type I diabetes (MedDRA 21.1 PT 10067584,**
- 28 **SOC 10027433)**
- 29 • Intervention(s): **once-daily pharmacotherapy with Elvanse (608137-32-2,**
- 30 **SUB32146) or Concerta (prolonged-release tablet, 298-59-9, SUB03254MIG) for a**
- 31 **duration of 6 months with initial dose optimization for 5-7 weeks, compared in a**
- 32 **randomized cross-over setup with blinded assessment; no placebo or control group**
- 33 **is applicable**
- 34 • Key Inclusion and Exclusion Criteria:
- 35 ○ **Principal inclusion criteria:**
- 36 ■ **Age 8-16.5 years at study entry;**
- 37 ■ **T1D diagnosed on the basis of clinical features, presence of**
- 38 **autoantibodies typical for type 1 diabetes (at least one of the**
- 39 **following: anti-GAD, ICA, IAA/IA2, ZnT8) and/or low C-peptide levels**
- 40 **(according to the laboratory standard appropriate for the assay**
- 41 **method) and criteria for the diagnosis of diabetes according to the**

criteria of the Polish Diabetes Association and international societies:

- an incidental glycemia ≥ 200 mg/dl and symptoms of hyperglycemia (such as increased thirst, polyuria, weakness) or
 - two times a fasting blood glucose ≥ 126 mg/dl or
 - a blood glucose ≥ 200 mg/dL in the 120th minute of an oral glucose load test or
 - HbA1c $\geq 6.5\%$.
- T1D diagnosed at least 12 months before recruitment;
 - T1D treated with functional intensive insulin therapy;
 - a diagnosis of ADHD according to DSM-5 criteria confirmed by a psychiatrist or a diagnosis of ADHD according to other criteria recognized in Poland, confirmed by an authorized person as consistent with DSM-5;
 - Polish citizenship and Polish health insurance.
- Principal exclusion criteria:
- Daily insulin dose < 0.3 j/kg and concomitant HbA1c measurement $\leq 6.5\%$ from the last 3 months (clinical partial remission of T1D);
 - Severely unsatisfactory glycemic control – mean HbA1c over the past year $\geq 12\%$ (not including HbA1c measurement at diagnosis of T1D);
 - Diagnosed intellectual or other disability that prevents participation in the trial or adherence to its therapeutic regimen;
 - Clinically apparent cardiovascular disease: recognized hemodynamically significant heart defect, advanced vascular atherosclerosis;
 - Diagnosis of other mental illness or disorder preventing participation in the trial, e.g. bipolar affective disorder, schizophrenia, other psychotic disorders, psychoactive substance abuse;
 - Diagnosed allergy or hypersensitivity to drugs used in pharmacological intervention -methylphenidate and/or lisdexamphetamine;
 - Language barrier making it impossible to conduct a full psychological consultation in Polish;
 - Lack of permanent residence in Poland;
 - Contraindications as reported for investigated drugs: documented hypertension (at least stage 2), positive family history for sudden cardiac deaths and atrial arrhythmias in relatives below 40 y.o., clinically evident glaucoma or abnormally elevated intraocular pressure, history of suicide attempts or present suicide intentions, oppositional defiant disorder, chronic motor tics or Tourette syndrome, pregnancy or breastfeeding, short stature, underweight

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3 86 ($\leq 3^{\text{rd}}$ percentile for reference percentile charts), epilepsy,
4 87 pheochromocytoma, substance abuse or positive drug test results,
5 88 prolonged treatment with sedative drugs (e.g., 1st generation
6 89 antihistamines);
7
8
9 90 ▪ Declared by the parents/legal guardians' inability or unwillingness to
10 91 come to the Center at the time specified by the protocol, in
11 92 particular - to pick up the Trial drugs at the dose adjustment stage
12 93 (the need to pick up 4-5 times over 6-8 weeks, each time within 2-3
13 94 days of receiving the recommendations);
14
15 95 ▪ Other reasons that, in the opinion of the attending physician, are
16 96 more likely to result in difficulties in maintaining the continuity of
17 97 the participant's participation in the trial or harm to the participant's
18 98 health in case of participation in the trial.
19
20
21 99 • Study Type: **interventional, open, randomized (block randomization stratified by**
22 100 **center), assessor masked, cross-over, phase II;**
23
24 101 • Date of First Enrollment: **anticipated 2023-09-01**
25
26 102 • Sample Size: **planned 150**
27
28 103 • Recruitment Status: **pending**
29
30 104 • Primary Outcome(s):
31
32 ○ **Change of ADHD symptom severity, measured as the difference in ADHD**
33 105 **symptom scores on the "inattention" and "hyperactivity/impulsivity" scales**
34 106 **of the Conners 3 questionnaire (completed by patient and parent/legal**
35 107 **guardian), before pharmacotherapy (after completion of PTBM) and the**
36 108 **end of the 6-month course of pharmacotherapy with LDX or MPH; similar**
37 109 **difference (before pharmacotherapy and after 6 months of therapy) for the**
38 110 **other drug, assessed by the investigator blinded to patient allocation.**
39
40 ○ **The number and frequency of adverse events (per patient-month) coded**
41 111 **following the MedDRA dictionary, in both cycles of pharmacotherapy.**
42
43 112 • Key Secondary Outcomes:
44
45 ○ **Improvement of metabolic control of T1D, quantified as:**
46 116 ▪ **The difference in HbA1c measured at the end of the MPH and LDX**
47 117 **treatment regimen compared to the measurement before**
48 118 **pharmacotherapy**
49
50 ▪ **The difference in the percentage of time patient spent in the**
51 119 **following ranges in 14 days at the end of a MPH and LDX**
52 120 **pharmacotherapy cycle, compared to 14 days prior**
53 121 **pharmacotherapy initiation:**
54 122 • **in target (70-180mg/dl)**
55 123 • **hypoglycemia (<70mg/dl)**
56 124 • **clinically significant hypoglycemia (<54mg/dl)**
57 125 • **hyperglycemia (>180mg/dl)**
58 126 • **significant hyperglycemia (>250mg/dl)**
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- 128 ▪ **The difference in mean glycemia and coefficient of variation of**
- 129 **glycemia (calculated as the ratio of the standard deviation of**
- 130 **glycemia to mean glycemia, expressed as a percentage) calculated**
- 131 **for 14 days at the end of the MPH and LDX pharmacotherapy**
- 132 **courses, compared to 14 days prior pharmacotherapy initiation**
- 133 ○ **Improvement of the subject's quality of life (QoL) from baseline, after**
- 134 **completion of PTBM and each pharmacotherapy course. The outcome will**
- 135 **be measured as the difference between the subject's QoL and diabetes-**
- 136 **specific QoL (PedsQL 3.2 questionnaires, completed by patient and**
- 137 **parent/legal guardian, assessed by an investigator blinded to patient**
- 138 **allocation)**
- 139 ○ **Number and percentage of trial participants achieving an improvement in**
- 140 **ADHD symptom severity of at least 1/3 of the baseline value at the end of a**
- 141 **given pharmacological intervention compared (assessed separately on the**
- 142 **basis of "inattention" AND "hyperactivity/impulsivity" scales) (endpoint**
- 143 **assessment by an investigator blinded to patient allocation).**
- 144 ● **Ethics Review: Approved (RNN/280/21/KE), 2022-06-14, Bioethics Committee at**
- 145 **the Medical University of Lodz, Józef Haller sq., 1B, 90-647 Łódź, Poland**
- 146 ● **Completion Date: LSLV planned 2026-08-01**
- 147 ● **Summary Results: Not available**
- 148 ● **IPD sharing statement: No; Individual Participant Data (with Protected Health**
- 149 **Information included) will be provided only in case of serious adverse events and**
- 150 **suspected unexpected serious adverse reactions and only to applicable regulators**
- 151 **and monitor institutions under appropriate regulations and applicable law.**

152 **SPIRIT 2013 additional requirements:**

- 153 ● **Role of study sponsor and funders, if any, in study design; collection, management,**
- 154 **analysis, and interpretation of data; writing of the report; and the decision to submit**
- 155 **the report for publication, including whether they will have ultimate authority over**
- 156 **any of these activities:**
- 157 ○ **Study sponsor (Medical University of Lodz) is directly involved in: trial**
- 158 **documentation preparation, management of electronic trial**
- 159 **documentation, providing randomization software, statistical analysis plan**
- 160 **preparation, pharmacovigilance and safety monitoring; Medical University**
- 161 **of Lodz hold ultimate authority over trial documentation preparation,**
- 162 **management of electronic trial documentation, providing randomization**
- 163 **software, statistical analysis plan preparation, pharmacovigilance and**
- 164 **safety monitoring, and guarantees all activities follow applicable**
- 165 **regulations.**
- 166 ○ **Study funder (Medical Research Agency) is directly involved in the financial**
- 167 **supervision of the trial, and holds ultimate authority in budget approval.**
- 168 ● **Composition, roles, and responsibilities of the coordinating centre, steering**
- 169 **committee, endpoint adjudication committee, data management team, and other**

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3 170 individuals or groups overseeing the Trial, if applicable (see Item 21a for data
4 171 monitoring committee):
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6 172 ○ **Coordinating centre: Medical University of Lodz Representatives (1), Clinical**
7 173 **Trials Unit Representatives (3); roles: preparation of Sponsor-Centers**
8 174 **agreements, preparation of registration documents; responsibilities:**
9 175 **supervision over clinical trial;**
10
11 176 ○ **Steering committee: Principal Investigator (1), Center Representatives (6),**
12 177 **Clinical Trials Unit Representatives (3); roles: coordination of screening and**
13 178 **trial procedures; responsibilities: organization and supervision over patient**
14 179 **workflow in centres involved with patient recruitment and interventions;**
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16 180 ○ **Endpoint adjudication committee: Polish Federation for Support for**
17 181 **Children and Adolescents with Diabetes (1); roles: masked assessment of**
18 182 **primary outcomes; responsibilities: providing assessor-blinded primary**
19 183 **outcomes assessment for all patients after the intervention;**
20
21 184 ○ **Data management team: Department of Biostatistics and Translational**
22 185 **Medicine (2 IT + 3 biostats); roles: preparation of data management plan**
23 186 **and data sharing policy, assistance with preparation of registration**
24 187 **documents and electronic trial documentation; responsibilities: supervision**
25 188 **over crucial informatics system for the clinical trial, statistical analysis of**
26 189 **clinical trial results following appropriate standards;**
27
28 190 ○ **Pharmacovigilance committee: Clinical Trials Unit staff (4), Principal**
29 191 **Investigator (1), Clinical Investigators (2); roles: assessment, classification,**
30 192 **reporting and submission of adverse events, drug safety monitoring and**
31 193 **reporting; responsibilities: monitoring of patient safety during the clinical**
32 194 **Trial;**
33
34 195 ○ **Quality assessment committee: Clinical Trials Unit Clinical Trials Unit (1);**
35 196 **roles: assessment of all trial documentation in the context of Good Clinical**
36 197 **Practice (GCP) and other appropriate ICH documentation, preparation, and**
37 198 **training of Standard Operating Procedures (SOP); responsibilities:**
38 199 **monitoring of clinical trial compliance with GCP and relevant SOP;**
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40 200 ○ **Legal department: Clinical Trials Unit (4); roles: preparation, review, and**
41 201 **negotiation of legal agreement; responsibilities: compliance of all trial**
42 202 **documentation with relevant regulations.**
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Line
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	S2: 5-8 S2: 10
	2b	All items from the World Health Organization Trial Registration Data Set	S2: 4-150
Protocol version	3	Date and version identifier	S2: 3
Funding	4	Sources and types of financial, material, and other support	569-570
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5-8 563-568
	5b	Name and contact information for the trial sponsor	S2: 14 S2: 16-19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	151-156 229-232 271-272 277-281 570-571 S2: 152-166
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the Trial, if applicable (see Item 21a for data monitoring committee)	S2: 167-201
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the Trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	87-144 S1: 58-121 S1: 299-410 S1: 637-673 S1: 885-897 S1: 944-983
	6b	Explanation for choice of comparators	323-355
Objectives	7	Specific objectives or hypotheses	145-148 289-322
Trial design	8	Description of trial design including type of Trial (eg, parallel group, cross-over, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	151-152 250-252 S2: 98-99
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	195-215
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	167-196
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	216-273 S2: 28-32
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	166-194 253-269 433-434 S2: 311-382 S2: 515-517 S2: 752-757
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	258-263 441-443 S2: 142-147
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the Trial	424-425
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	289-355 S2: 103-142

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and wash-outs), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 Table 1 224-273
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	378-398 S2: 101
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	151-156 158-164 196-226 387-398
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	274-281
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	274-281
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	274-281
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	282-288 S2: 28-32 S2: 103-142 S2: 179-182
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the Trial	282-288
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	289-323 323-355 S2: 122-298 S2: 420-431 S2: 438-458 S2: 674-884 S2: 983-1195
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	237-242 369-374
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	399-403 S2: 174-150 S2: 183-188
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	356-377
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	356-377
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	369-374
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	S2: 167-201
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the Trial	423-434
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	425-434
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	404-410
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	416-418 S2: 143-144

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	420-422
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	218-225 S1: 509-537 S1: 1226-1259
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	218-225 S1: 412-419 S1: 476-484 S1: 898-903 S1: 1214-1221
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the Trial	286-288 334-355 366-368 399-403 424-433 S1: 491-503 S1: 538-600 S1: 892-897 S1: 1261-1322 S2: 147-150
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall Trial and each study site	571
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	405-410 424-433 S2: 183-188
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	438-443 S1: 223-225
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	437-442 S1: 51-57 S1: 380-382 S1: 470-475 S1: 1209-1213
	31b	Authorship eligibility guidelines and any intended use of professional writers	564-569
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	439-443 S1: 491-503 S1: 538-600 S1: 892-897 S1: 1261-1322
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	S1: 30-601 S1: 616-906 S1: 922-1322
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current Trial and for future use in ancillary studies, if applicable	S1: 412-419 S1: 476-484 S1: 898-903 S1: 1214-1221

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BMJ Open

LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – protocol for a multicentre, randomized cross-over clinical trial in an outpatient telemedicine-supported setting

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Manuscripts

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4 1 Title: LisdexAmphetamine versus Methylphenidate for Pediatric
5 2 Patients with Attention-Deficit Hyperactivity Disorder and Type 1
6 3 Diabetes (LAMAinDiab) – protocol for a multicentre, randomized
7 4 cross-over clinical trial in an outpatient telemedicine-supported
8 5 setting
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39 Word count: 4060/4000

40 **ABSTRACT**

41 **Introduction**

42 Attention deficit hyperactivity disorder (ADHD) affects 5-10% of pediatric population and is
43 reportedly more common in children with type 1 diabetes (T1D), exacerbating its clinical
44 course. Proper treatment of ADHD in such patients may thus provide neurological and
45 metabolic benefits. To test this, we designed a non-commercial 2nd phase clinical trial
46 comparing the impact of different pharmacological interventions for ADHD in children with
47 T1D.

48 **Methods and analysis**

49 This is a multicentre, randomized, open-label, cross-over clinical trial in children and
50 adolescents with ADHD and T1D. The Trial will be conducted in four reference pediatric
51 diabetes centres in Poland. Over 36 months, eligible patients with both T1D and ADHD (aged
52 8-16.5 years, T1D duration >1 year) will be offered participation. Patients's guardians will
53 undergo online once-weekly training sessions behavior management for ten weeks.
54 Afterward, children will be randomized to methylphenidate (MPH, long-release capsule, doses
55 18-36-54mg) versus lisdexamphetamine (LDX, 30-50-70mg). Pharmacotherapy will continue
56 for 6 months before switching to alternative medication. Throughout the Trial, the
57 participants will be evaluated every three months by their diabetologist and online
58 psychological assessments. The primary endpoint (ADHD symptom severity, Conners 3.0
59 questionnaire) will be assessed by a blinded investigator. Secondary endpoints will include
60 HbA1c, CGM indices, and Quality of Life (PedsQL).

61 **Ethics and dissemination**

62 The trial is approved by Bioethical Committee at Medical University of Lodz and Polish
63 regulatory agency (RNN/142/22/KE, UR/DBL/D/263/2022). The results will be communicated
64 to the research and clinical community, and to Polish agencies responsible for healthcare
65 policy. Patient organizations focused on pediatric T1D will be notified by a consortium
66 member. We hope to utilize the trial's results to promote collaboration between mental
67 health professionals and diabetes teams, evaluate the economic feasibility of using LDX in
68 patients with both diseases and in the long run improve ADHD treatment in children with T1D.

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3 70 **Strengths and limitations of this study**
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5 71 **Strengths:**

- 6 72 • Blinded assessment of primary endpoint, use of structured and validated questionnaires
7 73 for diagnosis and assessment.
8 74 • Direct comparison of drugs via cross-over design with planned dose-optimization protocol.
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11 75 **Limitations:**

- 12 76 • Patients and physicians not blinded to the drug, possible expectation bias.
13 77 • A moderate risk of selection bias – exclusion of patients with more complex psychiatric
14 78 phenotypes. Caregivers and patients reluctant to stimulant medication drugs may be
15 79 unwilling to participate.
16 80 • Small differences in the efficacy of active compound release between the tested drugs
17 81 (possible active dose-related bias in clinical effectiveness), dose optimization for LDX not
18 82 including all market-available intermediate doses.
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24 84 **Keywords:**

25 85 Attention-deficit hyperactivity disorder, type 1 diabetes, methylphenidate,
26 86 lisdexamphetamine, clinical trial, HbA1c,
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87 Introduction

88 ADHD effect on type 1 diabetes treatment

89 Type 1 diabetes (T1D) is a common disease affecting over one million children worldwide, with
90 an age-standardised incidence of 31/100,000 in Europe, and 16/100,000 in Poland (0-19
91 years)(1,2).

92 Recent advantages in medical technology improved glycemic control and significantly reduced
93 rates of diabetes complications(3,4). However, state-of-art therapy of T1D requires frequent
94 blood glucose monitoring, counting of carbohydrates intake and adjustments of administered
95 insulin doses. These and other activities put considerable burden on the patient and their
96 guardians. To benefit from such intensive treatment, a child needs efficient executive
97 functioning and high level of self-control – and those who lack those abilities might face the
98 gap between expected and achieved outcomes.

99 In particular, comorbid psychological and neurodevelopmental disorders were shown to
100 impair diabetes management(5–8). A prime example is attention deficit hyperactivity disorder
101 (ADHD), which affects 5-10% of children(9) and is reported to be up to 35% more frequent
102 (OR 1.35; 95% CI: 1.08–1.73) in patients with T1D compared to healthy peers(10). A Swedish
103 active screening of children with T1D showed that among children with newly diagnosed
104 ADHD, 77.8% had inadequate metabolic control (mean HbA1c>8.6%) compared to 42.9% in
105 the group of children with treated ADHD(11). Association between ADHD and poor T1D
106 control were also reported by German and Israeli studies(12,13). In addition, those patients
107 experience an elevated risk of life-threatening episodes of severe hypoglycemia or
108 ketoacidosis, resulting in prolonged hospitalizations(10,14,15) and long-term complications,
109 such as diabetic nephropathy(5). In that perspective the need for evidence regarding the
110 effectiveness and safety of ADHD treatment in pediatric T1D emerges as a pertinent clinical
111 challenge.

112 Current ADHD treatments and their effects on type 1 diabetes

113 No randomized clinical trials (RCT) have been conducted regarding the effectiveness and
114 safety of ADHD treatment in those with coexisting T1D. Therefore, despite the tremendous
115 impact that both conditions have on patients' everyday life, current clinical guidelines on the
116 psychological management of T1D do not address the problem of ADHD(16).

117 Many European therapeutic guidelines recommend environmental modifications or
118 psychosocial intervention as first-line treatment for children with ADHD(17–19). Parent
119 training in behavior management (PT) is a psychosocial intervention aimed at improving
120 caregiver's understanding of ADHD symptoms and helping them acquire skills to deal with
121 everyday challenging behavior and support child development. Although PT improves
122 parenting and reduces conduct problems, meta-analyses found no effect of PT on core ADHD
123 symptoms when raters were blinded to the treatment allocations(20). If, despite PT,
124 symptoms of ADHD persist and cause significant impairment of everyday functioning,
125 pharmacotherapy is recommended.

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3 126 Preferred medications include stimulants, which showed better efficacy (higher effect sizes)
4 127 on ADHD core symptom reduction and easier dose optimization protocols than non-
5 128 psychostimulating medications(21,22). Two psychostimulants with best evidence for
6 129 effectiveness and tolerability are methylphenidate (MPH) and lisdexamphetamine (LDX). LDX,
7 130 contrary to MPH, is an inactive prodrug that requires enzymatic conversion, resulting in an
8 131 extended and more stable acting time (~13h). In most international guidelines, LDX is advised
9 132 as first line treatment comparable to long-acting MPH, or as a secondary drug after treatment
10 133 failure with previous MPH medication attempts(22). In Poland LDX is neither reimbursed by
11 134 the National Health Fund (NHF) nor commercially available. As a result, long-acting MPH
12 135 formulations are considered the first-line pharmacotherapy for ADHD(23).

13 136 Limited retrospective data demonstrates that patients with ADHD and T1D treated with
14 137 stimulants show lower HbA1c ($8.1\pm 1.0\%$) compared to children that were diagnosed but not
15 138 treated pharmacologically ($8.5\pm 1.1\%$)(24). At the same time, others reported higher blood
16 139 pressure and no difference in metabolic control(12,13). However, generalization of those
17 140 results remains limited due to the low sample size, lack of evidence from RCTs, and no direct
18 141 comparisons between LDX and MPH. In conclusion, there is a lack of data on the safety and
19 142 effectiveness of ADHD medication in children with T1D regarding the effect on ADHD
20 143 symptoms, quality of life, and metabolic control.

21 144 **The aim of the Study**

22 145 The Trial aims to compare the safety and efficacy of ADHD treatment with LDX or MPH in
23 146 children and adolescents with ADHD and T1D.

24 147 **Methods and analysis**

25 148 **Study design and population**

26 149 LAMAIinDiab is a phase 2 randomized cross-over openlabel clinical trial with blinded endpoint
27 150 assessment. Cross-over design was chosen based on the sample size analysis, as well as for
28 151 ethical reasons – to provide each participant with an active drug with proven efficacy in ADHD.
29 152 The project is funded by the Medical Research Agency (pol. “Agencja Badań Medycznych”),
30 153 which supports non-commercial clinical trials in Poland through open calls. Upon grant
31 154 application, the project consortium was established, and four recruiting sites – that
32 155 collectively provide care for ~25% of national pediatric population with T1D(25,26) – were
33 156 declared.

34 157 **Patient and Public Involvement statement**

35 158 The project was consulted with and supported by a national patient organization (Polish
36 159 Federation for Support of Children and Adolescents with Diabetes, “Diabetycy.eu”), which
37 160 entered the project’s consortium. Clinical trial’s design and protocol were thoroughly
38 161 consulted with the organization, and its representative (MZ) was included among the authors
39 162 to acknowledge her input. Subsequently, the organization’s qualified representatives agreed
40 163 to play the roles of independent investigators blinded to the treatment allocation and perform
41 164 ADHD symptom assessments for participating children.

42 165 **Inclusion and exclusion criteria**

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3 166 Principal inclusion criteria:
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- 5 167 • Age 8-16.5 years at trial entry;
6 168 • T1D diagnosed according to National and International Guidelines(27)(28) at least 12
7 169 months before recruitment, treated with functional intensive insulin therapy,
8 170 • ADHD diagnosis according to 5th Edition Diagnostic and Statistical Manual of Mental
9 171 Disorders (DSM-5)(29) or International Statistical Classification of Diseases (ICD-10)(30)
10 172 and confirmed as consistent with DSM-5 by a psychiatrist;
11 173 • Polish citizenship and health insurance.

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15 174 Principal exclusion criteria:
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- 17 175 • Clinical partial remission of T1D (daily insulin dose<0.3 units per kilogram and concomitant
18 176 HbA1c measurement $\leq 6.5\%$ from the last 3 months) or severely unsatisfactory glycemic
19 177 control (mean HbA1c over the past year $\geq 12\%$, excluding HbA1c measurement at T1D
20 178 diagnosis);
21 179 • Clinically apparent or previously-diagnosed cardiovascular disease: hemodynamically
22 180 significant heart defect, advanced vascular atherosclerosis, or documented hypertension
23 181 (at least stage 2);
24 182 • Diagnosed intellectual disability or other disability that prevents patient adherence to the
25 183 therapeutic regimen; history of other mental illness or disorder preventing participation
26 184 in the trial, e.g. bipolar disorder, schizophrenia, other psychotic disorders, history of
27 185 suicide attempts or present suicide intentions, psychoactive substances abuse;
28 186 • Contraindications to either studied drug.
29 187 • Language barrier making it impossible to conduct a full psychological consultation in
30 188 Polish, lack of permanent residence and national insurance in Poland;
31 189 • Inability of the parents/legal guardians' to come to the Centre at the time specified by the
32 190 protocol, in particular – to pick up the study drugs at the dose adjustment stage (the need
33 191 to pick up 4-5 times over 6-8 weeks, each time within 2-3 days of receiving the
34 192 recommendations);
35 193 • Other reasons that, in the opinion of the attending physician, are more likely to result in
36 194 difficulties in maintaining the participant's participation in the trial or harm to the
37 195 participant's health in case of participation in the trial.

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45 196 **Setting**
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47 197 The Trial will be conducted in 4 pediatric diabetology centres, and apply telemedical tools to
48 198 facilitate recruitment, improve compliance and reduce the burden on participants and their
49 199 families. The participating centres provide coordinated pediatric diabetes care for their
50 200 respective voivodeships (regions of Poland):

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53 201 • Lodzkie voivodeship: Department of Pediatrics, Diabetology, Endocrinology and
54 202 Nephrology, Pediatric Centre of the Central Clinical Hospital of the Medical University of
55 203 Lodz;
56 204 • Silesian voivodeship: Department of Children's Diabetology, Medical University of Silesia,
57 205 Upper Silesian John Paul II Child Health Centre;

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3 206 • Pomeranian voivodeship: Department of Pediatrics, Diabetology, and Endocrinology of the
4 207 Medical University of Gdansk, University Clinical Centre in Gdansk;
5
6 208 • Opole voivodeship: Department of Pediatrics of the Institute of Medical Sciences of the
7 209 University of Opole (Department of Pediatrics and the Diabetology Clinic for Children of
8 210 the University Clinical Hospital in Opole).

10 211 Information about the centres was published on the project's website - lamaindiab.umed.pl.
11 212 Pediatric diabetology centres included in the trial are public care providers – the trial visits and
12 213 procedures will be carried out as add-ons to routine visits related to the management of
13 214 diabetes. Pediatric healthcare in Poland is tax-financed by the National Health Found (NHF)
14 215 and provides universal, free-of-charge care for all children registered in Poland and their
15 216 caregivers.

19 217 **Summary of trial procedures**

20 218 Patients with ADHD and T1D, meeting the clinical trial's inclusion criteria may enroll into the
21 219 Trial in the designated reference centres. First, their guardians will receive information about
22 220 the study from the centre's representative via phone, followed by complete Information and
23 221 Consent forms sent to agreed mail address. During the next routine outpatient consultation,
24 222 the guardians and children will thoroughly discuss the information provided with an
25 223 investigator. After answering any questions related to the study and its protocol, the
26 224 investigator will verify inclusion and exclusion criteria and obtain signed informed consent
27 225 form in line with current regulations (from both parents and children ≥ 13 y.o.). After successful
28 226 recruitment, study procedures will be initiated. Simplified patient's course in the clinical trial
29 227 is demonstrated in Figure 1.

33 228 [FIGURE 1]

34 229 Each patient will begin the Trial starting with the enrollment appointment, followed by a
35 230 baseline assessment by a diabetologist and a psychological evaluation. At this stage, all trial
36 231 participants will be provided with the following devices: pre-configured tablets with
37 232 appropriate telecommunication software and prepaid internet access, wrist accelerometers,
38 233 and blood pressure monitors. All devices will be provided by the Medical University of Lodz to
39 234 assist participants and their parents in following the study procedures and data collection.
40 235 Additionally, willing patients who did not qualify for reimbursement will be provided with
41 236 continuous glucose monitoring (CGM) sensors and receivers and instructed in their use.

42 237 Next, the patient's parents/legal guardians will participate in a PT program of 10 themed
43 238 online workshops (90 minutes long) led by psychotherapists and supplemented with
44 239 homework and educational materials. PT aims to provide immediate educational and
45 240 behavioral support for the child's caretakers by educating them about ADHD and providing
46 241 tools and skills to understand and modify the child's behaviors and was demonstrated to
47 242 strengthen family bonds and improve adherence to future pharmacotherapy. To successfully
48 243 complete this phase of the Trial, participant's guardians must participate in at least 8 meetings
49 244 – with a possible revisit of the missed ones in another cycle.

50 245 After completion of PT, each participant will repeat the psychological evaluation to assess the
51 246 effects of PT intervention alone on ADHD symptoms severity. Those with sustained clinically-
52 247 significant ADHD symptoms will be qualified for pharmacological intervention. Possible

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3 248 contraindications for pharmacotherapy will be assessed during the next diabetological visit.
4 249 The add-on procedures will include urine tests (pregnancy and panel test for substance use),
5 250 ECG with QT segment assessment (to exclude long QT syndrome) and ophthalmological
6 251 consultation (to exclude glaucoma). Subsequent and final assessment and qualification will be
7 252 performed by psychiatrist during an online consultation. Afterward, each participant starting
8 253 pharmacotherapy will be randomized using a digital randomization system to receive either
9 254 MPH or LDX as the first drug.

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13 255 The dose will be optimized during up to four biweekly psychiatric consultations in a flexible
14 256 manner (allowing both one-step increase and decrease between set minimum and maximum
15 257 dose for each studied drug). After the maximum tolerated dose is established, patients will
16 258 continue pharmacotherapy for 6 months. During that time, treatment safety and efficacy will
17 259 be evaluated twice - after first 3 months by psychological and diabetes care team's evaluation
18 260 (with small dose adjustments allowed) and after full course (6 months) of therapy. On-demand
19 261 psychiatric consultations will be allowed. In addition, during both diabetological visits each
20 262 participant will donate a dry blood sample for evaluation of the concentration of an allocated
21 263 drug, and another sample will be self-collected on the day of the final psychological
22 264 assessment for that arm to ensure that endpoint measurements are not biased by incidental
23 265 non-adherence. After the last evaluation, participants will return the unused drug to their
24 266 diabetes care centre and will begin a wash-out period.

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29 267 Qualification for the second arm of pharmacotherapy will be based on the same procedures
30 268 and consultations which will be performed in parallel with the last diabetological assessment
31 269 in the first arm. Final switch and start of the second drug (LDX or MPH) will be based on
32 270 psychiatrist decision. Dose adjustment, safety and efficacy monitoring will follow the same
33 271 procedures over the next 6 months. Schedule of the Trial's procedures was presented in
34 272 Supplementary Table 1.

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38 273 At the end of patient's participation in the Trial, all the devices will be returned to the
39 274 University, and the last safety and efficacy interview will be performed. All the patients will
40 275 receive further treatment recommendations at NHF facilities.

41 276 **Randomization**

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43 277 The starting drug will be determined using block randomization stratified by the trial centre in
44 278 a 1:1 ratio between MPH and LDX. The risk of randomization error will be minimized by using
45 279 a user-friendly "Randomizer" IT tool provided by the Sponsor, integrated with the eCRF. In the
46 280 event of unexpected randomization difficulties (e.g., lack of internet access or other technical
47 281 problems), centre's trial-coordinator may request randomization via backup randomization
48 282 list available only for sponsor's representative, re-randomization or patient's withdrawal.

49 283 **Blinding**

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53 284 The participant allocation is open both to the participant and their guardians as well as their
54 285 attending physician (diabetologist and psychiatrist alike). Blinding at participant level was
55 286 considered but decided against due to practical reasons (i.e. costs and difficulties in producing
56 287 effective over-encapsulation, high risk for spontaneous unblinding due to differences in
57 288 pharmacokinetics of the studied drugs). However, the people assessing the primary outcome

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3 289 (i.e. ADHD symptom severity) will be blinded to the allocation and operating independently
4 290 from the care centres. No exceptions or unblinding options are planned for those researchers
5 291 as their assessment serves mostly research purpose, and data collected by them are reviewed
6 292 by unblinded clinicians.

9 293 **Endpoints and analysis**

10 294 The **primary endpoints** of the Trial are:

- 12 295 1. Efficacy, defined as change in the severity of ADHD symptoms ("inattention" and
13 296 "hyperactivity/impulsivity" measured by Conners 3 questionnaire) compared between
14 297 LDX vs. MPH.
- 16 298 2. Safety, defined as frequency of MedDRA-defined adverse events for both drugs.

18 299 For each participant, we will calculate the difference in questionnaire scores ("inattention"
19 300 and "hyperactivity/impulsivity") at the end of each arm versus the initiation of drug therapy
20 301 (before first drug). Separate comparisons will be made for each subscale and informant
21 302 (guardian/child).

24 303 Safety analysis will report the number of recorded events by type and severity and the
25 304 incidence rate (the number of events divided by the number of patient-months of
26 305 observation).

29 306 The **secondary endpoints** of the Trial are (all compared between LDX and MPH arms):

- 31 307 1. Diabetes control, as measured by HbA1c and CGM-derived time in target range, mean
32 308 sensor glucose, and coefficient of variation, before and after treatment with each of
33 309 investigated drugs;
- 35 310 2. General and diabetes-related quality of life (measured with PedsQL questionnaires),
36 311 before and after treatment with each of investigated drugs;
- 37 312 3. Number and percentage of trial participants that achieved improvement of ADHD
38 313 symptoms (Conners 3 "inattention" and "hyperactivity/impulsivity") defined as 33%
39 314 reduction in scale values compared to baseline.

42 315 The **exploratory endpoints** of the Trial are:

- 44 316 1. Difference between LDX vs. MPH in school attendance during the month preceding the 6-
45 317 month drug evaluation;
- 46 318 2. Difference between LDX vs. MPH in physical activity (daily steps, % of time in moderate-
47 319 to-vigorous physical activity) and sleep (duration, latency, efficiency) indices;
- 49 320 3. Differences between baseline assessment and after PT completion concerning: in ADHD
50 321 symptoms severity (Conners 3 "inattention" and "hyperactivity/impulsivity"), HbA1c and
51 322 CGM-derived glycemic control (time in range, mean sensor glucose, coefficient of
52 323 variation);
- 54 324 4. Difference between LDX vs. MPH in frequency (number of events per patient-months) of
55 325 acute diabetes complications (severe hypoglycemia, ketoacidosis) and hospitalizations,
56 326 and number of days spent in inpatient care (number of days per patient-months).

59 327 **Tools and parameters used during the Trial**

328 During in-patient visits in the Trial, standard procedures will be performed, including
329 anthropometric, heart rate, and blood pressure measurements. Applicable values will be
330 referenced with Polish percentile charts.

331 ADHD symptoms will be measured using The Conners' Rating Scales (The Conners 3.0 scales,
332 Polish version) completed by parents (Conners 3.0-P) and children (Conners 3.0-
333 SR). The Conners' Rating Scales are validated and most commonly used tools to assess
334 difficulties in children and adolescents with ADHD in research and clinical settings worldwide.
335 The Polish version of Conners 3.0 has proven high psychometric reliability and validity. In the
336 Trial, we will focus on changes in content scales of "Inattention" and
337 "Hyperactivity/Impulsivity", two core domains of ADHD symptoms by DSM-5(29).

338 Diabetes control will be assessed using HbA1c measured in local laboratories using methods
339 concordant with the NGSP program. Moreover, patients will be instructed to use continuous
340 glucose monitoring (CGM) according to their leading physicians' recommendations and
341 generated data will be collected during diabetes check-ups. In Poland, CGM is reimbursed in
342 the form of intermittently-scanned CGM, with possible extension into real-time CGM for those
343 with impaired awareness of hypoglycemia. If available, CGMs will be linked with appropriate
344 devices: insulin pumps, CGM readers, mobile phones. CGM data will be backed up and
345 processed using GlyCulator 3.0 platform(31). For wrist accelerometer data, manufacturer-
346 provided software will be used to collect the data for further analysis.

347 Patient's quality-of-life (QoL) will be measured using the Pediatric Quality of Life Inventory 3.2
348 Core (PedsQL QoL) and Diabetes Module (PedsQL diab)(32). The PedsQL is the most common
349 tool to measure QoL in the pediatric population. The PedsQL Diabetes Module allows focusing
350 on T1D-specific issues, especially relevant for the ADHD interaction with T1D self-control.
351 PedsQL QoL and diab have been translated into Polish and validated for academic and
352 commercial use.

353 During the drug dose-optimization period, patients will be tasked with performing self-
354 assessment, including self-monitoring of blood pressure using automated monitors, diabetes
355 monitoring with CGM, and activity monitoring using a wrist accelerometer. Blood pressure
356 monitors data will be periodically uploaded into a central data repository integrated with
357 electronic case report forms (eCRF), while wrist accelerometry will be stored and analysed at
358 the Trial completion. CGM data will be backed up on in-patient clinic visits using appropriate
359 software in each centre.

360 **Statistical analysis**

361 The primary outcome will be compared between the LDX and MPH group using paired t-tests
362 and multivariable regression models to account for clinical covariates. Sensitivity analysis will
363 be performed for primary and secondary endpoints for the subgroup of patients with no
364 imputed data.

365 For each intervention, the % of reported adverse events will be reported with the relevant
366 statistics for paired comparisons (Chi², p), and for the entire table (T_{MB} , p). The incidence rates
367 for individual adverse events will be compared with appropriate statistical tests (Poisson test

368 or equivalent). In addition, each type of event will be compared using the McNemar test, and
369 the frequencies of different events using the McNemar-Bowker global symmetry test.

370 Treatment safety will be assessed and reported following standard procedures and coded
371 using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and WHO severity
372 scale, and recorded in eCRF.

373 Safety and efficacy endpoints will be analysed using data from patients who completed both
374 planned treatments, independent of potential protocol deviations (i.e., population "as
375 treated"). Data of patients lost to follow-up will be filled in on the basis of last-observation
376 carried forward, provided that they have at least one complete timepoint of outcome
377 measures on the current treatment. Patients with deviations from protocol leading to no
378 outcome data will not be included in efficacy analyses.

379 The secondary and exploratory endpoints will be evaluated using the appropriate statistical
380 methods for either continuous (paired t-test, linear regression) or nominal variables
381 (McNemar test). Interim analyses were not planned within this study.

382 **Sample size estimation**

383 To our knowledge, at the time of planning this Trial, no trial with equivalent design and
384 outcome measures in this population was published. Thus, we calculated the sample size to
385 allow for detection of a moderate difference (0.33 standard deviations) difference in score
386 changes between LDX vs. MPH for the key Conners 3 measures(33). Such difference was
387 deemed clinically-impactful by the clinical team designing the trial. To estimate the sample
388 size, we assumed significance threshold of $\alpha=0.05$, the statistical power of 80%. The risk
389 of applying multiple tests (each scale in each type of responder – four in total) was assessed
390 as minimal due to high intercorrelations among those measures. As such, no alpha adjustment
391 was planned. Such assumptions yielded the minimum number of participants of 89 (rounded
392 to 90). The risk of drop-out during pharmacotherapy was assessed as considerable (~33%) due
393 to the challenging population of interest (children with ADHD and T1D, with ADHD possibly
394 present in parents) and known side effects of tested medications. Thus, the target number of
395 pharmacologically-treated children was planned at 135, and 150 recruited given that up to
396 10% might be disqualified from pharmacotherapy due to drug contraindications or
397 considerable improvement after PT. Assuming recruitment success at 80% (considerable
398 benefit for patients, access to a drug unavailable in Poland, coordinated diabetes and
399 psychiatric care), we estimated that 190 children that should be approached. Based on the
400 general prevalence of ADHD in the pediatric population, the number of patients with T1D to
401 screen for ADHD would be at least 4000 – which was a number of patients supervised by the
402 4 Trial centres.

403 **Data entry and storage**

404 Patient data collected during the clinical Trial will be stored within the electronic trial
405 documentation database, following appropriate regulations, with data access provided to
406 appropriate trial personnel. Reported, presented, and published data will be anonymized. The
407 clinical trial records will be stored for 25 years after trial completion.

408 **Trial monitoring**

409 Trial monitoring will follow adequate international and national clinical trial regulations.
410 Sponsor's representatives will visit each site, discuss the clinical trial course, review and
411 validate relevant records, and verify all reference centres' that partake in the clinical trial.
412 National regulatory authorities may request access to research documentation, source
413 documents, research personnel, and facilities. The Sponsor will be notified of any centre's
414 audits by regulatory agencies, and copies of audit reports will be transferred accordingly.

415 **Trial timeline**

416 Planned date for starting the study is 1.01.2024, but may be prone to change following logistic
417 reasons. The trial is planned to last 48 months, setting the tentative end date of the study at
418 1.12.2027.

419

420 **Ethics and dissemination**

421 **Ethical considerations**

422 The clinical trial follows principles of the Helsinki Declaration, current Good Clinical Practice
423 guidelines, and other applicable regulations. The clinical trial has been registered in European
424 Union Drug Regulating Authorities Clinical Trials Database (no. 2022-001906-24) and in
425 ClinicalTrials.gov (NCT05957055). The clinical trial was approved by the Bioethical Committee
426 at Medical University of Lodz (agreement no. RNN/142/22/KE), and the Polish Office for
427 Registration of Medicinal Products, Medical Devices and Biocidal Products
428 (UR/DBL/D/263/2022). All participants of the clinical trial are insured within the appropriate
429 insurance agreements (policy no. COR233280) and signed informed consent forms from them
430 and their parents will be collected before trial procedures. All changes in the Trial are subject
431 to ethical and regulatory review before their incorporation into the clinical trial.

432 **Safety during and post intervention**

433 Before the intervention, the treatment of coexisting diseases will be recorded in the eCRF and
434 continued as is or appropriately modified by the respective specialist. All adverse events will
435 be documented in the electronic trial documentation using MedDRA v24.1 and graded using
436 applicable WHO standards, with SAE reported within 24 hours since the occurrence and
437 evaluated by Safety Monitoring Team (SMT). In case of a SUSAR, the SMT follows the Council
438 for International Organizations of Medical Sciences forms and reports it to appropriate
439 authorities within 15 days (or 7 in case of threat to the life or death of the patient) from
440 receiving the report, following the data transfer procedure with the applicable law. The SMT
441 will provide an annual patient safety report throughout the clinical trial, including appropriate
442 information on treatment safety. The Sponsor holds the right to pause or discontinue part of
443 the trial, the entire trial, or the participation of an individual patient.

444 After trial completion, all the patients will receive further treatment instructions, prescription
445 for ADHD treatment and referral to appropriate health provider facilities. Reference
446 diabetology centres will provide continued diabetes care under NHF.

447 **Dissemination plan**

448 Results will be submitted for publication in leading international scientific journals in diabetes
449 care, endocrinology and psychiatry. Results will also be shared during relevant national and
450 international congresses and conferences. The cooperation between the Sponsor and patient
451 organization (affiliation 13) will be continued after the Trial's completion to increase
452 awareness of the impact of psychiatric diseases in patients with T1D. The study's results will
453 also be communicated to the funding agency and national healthcare policy makers.

454 **Discussion**

455 Despite the favorable opinion of the Polish Agency for Health Technology Assessment and
456 Tariff System, LDX is still unavailable for Polish patients outside this clinical trial. We will
457 provide data collected during this Trial for consideration of the Agency, to promote discussion
458 about the availability of LDX and advocate for it being widely accessible (if not reimbursed).
459 We will also perform a specific cost-effectiveness analysis for the particular population of
460 children with ADHD and T1D, and investigate possible costs and benefits of considering LDX
461 as a first-line treatment in this group of patients, justified by the system savings provided by
462 possibly-improved diabetes control.

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41

42 598 **Author contribution:** AM, JC, HKK, WF, AB, KB – written the article, prepared the clinical
43 599 trial protocol; WF, AB, AM, KB – supervised the clinical trial registration; EK – translated the
44 600 clinical trial protocol and written the supplementary materials; BM, ASz, ACh, PJCh, MM, IM,
45 601 AK, TW, WF, AB – consulted the manuscript and the clinical trial protocol; MZ –supervised
46 602 patients consultation of the clinical trial. All authors reviewed the results and approved
47
48
49 603 the final version of the manuscript. We comply to the ICMJE guidelines.

50
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53
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60

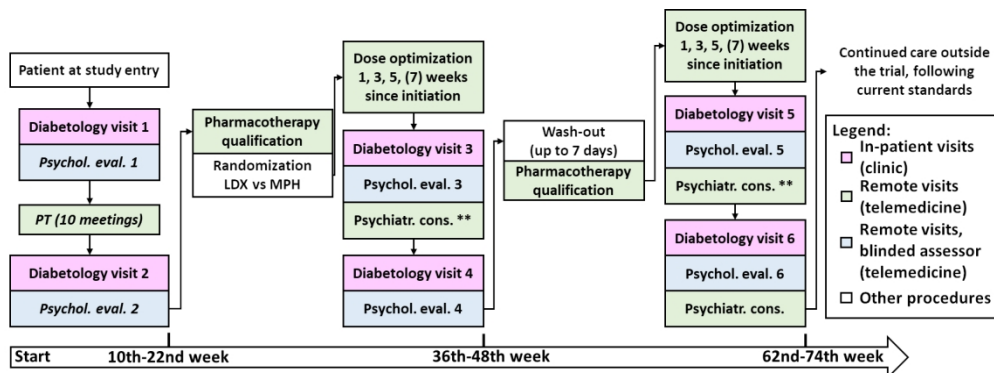


Figure 1. Simplified study design flowchart. PT – parental training, LDX – lisdexamphetamine, MPH – methylphenidate. ** - if needed on-demand consultation

315x117mm (150 x 150 DPI)

- 1 **Supplementary Table 1.** Study schedule. The order of treatment (A/B) will be decided at randomization (allocation step). Names of visits corresponding to
 2 Figure 1 are included.

		STUDY PERIOD								
		Enroll	PT	Allocate	Post-allocation					
DURATION		1 week	10-22 weeks	1 week	First treatment (6 months)			Second treatment (6 months)		
ENROLLMENT	Eligibility screen	X		X			X			
	Informed consent	X								
	Randomization (to A/B)			X						
INTERVENTION	Parent training in behaviour management		X							
	Cross-over	MPH			A	A	A	B	B	B
		LDX				B	B	B	A	A
ASSESSMENTS	Conners 3, PedsQL questionnaires	Psychological evaluation 1		Psychological evaluation 2		Psychological evaluation 3	Psychological evaluation 4		Psychological evaluation 5	Psychological evaluation 6
	Diabetes control (HbA1c, CGM)	Diabetological visit 1		Diabetological visit 2		Diabetological visit 3	Diabetological visit 4		Diabetological visit 5	Diabetological visit 6
	Anthropometric, BP, HR measurement									
	Urine tests, ECG with QT segment assessment, ophthalmologic consultation									
	Psychiatric consultation			LDX/MPH qualification	Dose optimization	*Additional dose adjustment		Dose optimization	*Additional dose adjustment	Referral to care under National Health Fund

- 3 *optional, up to the Investigator, only lowering of dose allowed



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Line
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	S2: 5-8 S2: 10
	2b	All items from the World Health Organization Trial Registration Data Set	S2: 4-150
Protocol version	3	Date and version identifier	S2: 3
Funding	4	Sources and types of financial, material, and other support	569-570
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5-8 563-568
	5b	Name and contact information for the trial sponsor	S2: 14 S2: 16-19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	151-156 229-232 271-272 277-281 570-571 S2: 152-166
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the Trial, if applicable (see Item 21a for data monitoring committee)	S2: 167-201
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the Trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	87-144 S1: 58-121 S1: 299-410 S1: 637-673 S1: 885-897 S1: 944-983
	6b	Explanation for choice of comparators	323-355
Objectives	7	Specific objectives or hypotheses	145-148 289-322
Trial design	8	Description of trial design including type of Trial (eg, parallel group, cross-over, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	151-152 250-252 S2: 98-99
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	195-215
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	167-196
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	216-273 S2: 28-32
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	166-194 253-269 433-434 S2: 311-382 S2: 515-517 S2: 752-757
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	258-263 441-443 S2: 142-147
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the Trial	424-425
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	289-355 S2: 103-142

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and wash-outs), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 Table 1 224-273
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	378-398 S2: 101
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	151-156 158-164 196-226 387-398
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	274-281
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	274-281
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	274-281
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	282-288 S2: 28-32 S2: 103-142 S2: 179-182
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the Trial	282-288
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	289-323 323-355 S2: 122-298 S2: 420-431 S2: 438-458 S2: 674-884 S2: 983-1195
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	237-242 369-374
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	399-403 S2: 174-150 S2: 183-188
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	356-377
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	356-377
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	369-374
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	S2: 167-201
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the Trial	423-434
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	425-434
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	404-410
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	416-418 S2: 143-144

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	420-422
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	218-225 S1: 509-537 S1: 1226-1259
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	218-225 S1: 412-419 S1: 476-484 S1: 898-903 S1: 1214-1221
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the Trial	286-288 334-355 366-368 399-403 424-433 S1: 491-503 S1: 538-600 S1: 892-897 S1: 1261-1322 S2: 147-150
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall Trial and each study site	571
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	405-410 424-433 S2: 183-188
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	438-443 S1: 223-225
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	437-442 S1: 51-57 S1: 380-382 S1: 470-475 S1: 1209-1213
	31b	Authorship eligibility guidelines and any intended use of professional writers	564-569
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	439-443 S1: 491-503 S1: 538-600 S1: 892-897 S1: 1261-1322
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	S1: 30-601 S1: 616-906 S1: 922-1322
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current Trial and for future use in ancillary studies, if applicable	S1: 412-419 S1: 476-484 S1: 898-903 S1: 1214-1221

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – protocol for a multicentre, randomized cross-over clinical trial in an outpatient telemedicine-supported setting

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Secondary Subject Heading:	Diabetes and endocrinology, Mental health
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4 1 Title: LisdexAmphetamine versus Methylphenidate for Pediatric
5 2 Patients with Attention-Deficit Hyperactivity Disorder and Type 1
6 3 Diabetes (LAMAinDiab) – protocol for a multicentre, randomized
7 4 cross-over clinical trial in an outpatient telemedicine-supported
8 5 setting
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39 Word count: 4105/4000

40 **ABSTRACT**

41 **Introduction**

42 Attention deficit hyperactivity disorder (ADHD) affects 5-10% of pediatric population and is
43 reportedly more common in children with type 1 diabetes (T1D), exacerbating its clinical
44 course. Proper treatment of ADHD in such patients may thus provide neurological and
45 metabolic benefits. To test this, we designed a non-commercial 2nd phase clinical trial
46 comparing the impact of different pharmacological interventions for ADHD in children with
47 T1D.

48 **Methods and analysis**

49 This is a multicentre, randomized, open-label, cross-over clinical trial in children and
50 adolescents with ADHD and T1D. The Trial will be conducted in four reference pediatric
51 diabetes centres in Poland. Over 36 months, eligible patients with both T1D and ADHD (aged
52 8-16.5 years, T1D duration >1 year) will be offered participation. Patients's guardians will
53 undergo online once-weekly training sessions behavior management for ten weeks.
54 Afterward, children will be randomized to methylphenidate (MPH, long-release capsule, doses
55 18-36-54mg) versus lisdexamphetamine (LDX, 30-50-70mg). Pharmacotherapy will continue
56 for 6 months before switching to alternative medication. Throughout the Trial, the
57 participants will be evaluated every three months by their diabetologist and online
58 psychological assessments. The primary endpoint (ADHD symptom severity, Conners 3.0
59 questionnaire) will be assessed by a blinded investigator. Secondary endpoints will include
60 HbA1c, CGM indices, and Quality of Life (PedsQL).

61 **Ethics and dissemination**

62 The trial is approved by Bioethical Committee at Medical University of Lodz and Polish
63 regulatory agency (RNN/142/22/KE, UR/DBL/D/263/2022). The results will be communicated
64 to the research and clinical community, and to Polish agencies responsible for healthcare
65 policy. Patient organizations focused on pediatric T1D will be notified by a consortium
66 member. We hope to utilize the trial's results to promote collaboration between mental
67 health professionals and diabetes teams, evaluate the economic feasibility of using LDX in
68 patients with both diseases and in the long run improve ADHD treatment in children with T1D.

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3 70 **Strengths and limitations of this study**
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5 71 **Strengths:**

- 6 72 • Blinded assessment of primary endpoint, use of structured and validated questionnaires
7 73 for diagnosis and assessment.
8 74 • Direct comparison of drugs via cross-over design with planned dose-optimization protocol.
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11 75 **Limitations:**

- 12 76 • Patients and physicians not blinded to the drug, possible expectation bias.
13 77 • A moderate risk of selection bias – exclusion of patients with more complex psychiatric
14 78 phenotypes. Caregivers and patients reluctant to stimulant medication drugs may be
15 79 unwilling to participate.
16 80 • Small differences in the efficacy of active compound release between the tested drugs
17 81 (possible active dose-related bias in clinical effectiveness), dose optimization for LDX not
18 82 including all market-available intermediate doses.
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24 84 **Keywords:**

25 85 Attention-deficit hyperactivity disorder, type 1 diabetes, methylphenidate,
26 86 lisdexamphetamine, clinical trial, HbA1c,
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87 Introduction

88 ADHD effect on type 1 diabetes treatment

89 Type 1 diabetes (T1D) is a common disease affecting over one million children worldwide, with
90 an age-standardised incidence of 31/100,000 in Europe, and 16/100,000 in Poland (0-19
91 years)(1,2).

92 Recent advantages in medical technology improved glycemic control and significantly reduced
93 rates of diabetes complications(3,4). However, state-of-art therapy of T1D requires frequent
94 blood glucose monitoring, counting of carbohydrates intake and adjustments of administered
95 insulin doses. These and other activities put considerable burden on the patient and their
96 guardians. To benefit from such intensive treatment, a child needs efficient executive
97 functioning and high level of self-control – and those who lack those abilities might face the
98 gap between expected and achieved outcomes.

99 In particular, comorbid psychological and neurodevelopmental disorders were shown to
100 impair diabetes management(5–8). A prime example is attention deficit hyperactivity disorder
101 (ADHD), which affects 5-10% of children(9) and is reported to be up to 35% more frequent
102 (OR 1.35; 95% CI: 1.08–1.73) in patients with T1D compared to healthy peers(10). A Swedish
103 active screening of children with T1D showed that among children with newly diagnosed
104 ADHD, 77.8% had inadequate metabolic control (mean HbA1c>8.6%) compared to 42.9% in
105 the group of children with treated ADHD(11). Association between ADHD and poor T1D
106 control were also reported by German and Israeli studies(12,13). In addition, those patients
107 experience an elevated risk of life-threatening episodes of severe hypoglycemia or
108 ketoacidosis, resulting in prolonged hospitalizations(10,14,15) and long-term complications,
109 such as diabetic nephropathy(5). In that perspective the need for evidence regarding the
110 effectiveness and safety of ADHD treatment in pediatric T1D emerges as a pertinent clinical
111 challenge.

112 Current ADHD treatments and their effects on type 1 diabetes

113 No randomized clinical trials (RCT) have been conducted regarding the effectiveness and
114 safety of ADHD treatment in those with coexisting T1D. Therefore, despite the tremendous
115 impact that both conditions have on patients' everyday life, current clinical guidelines on the
116 psychological management of T1D do not address the problem of ADHD(16).

117 Many European therapeutic guidelines recommend environmental modifications or
118 psychosocial intervention as first-line treatment for children with ADHD(17–19). Parent
119 training in behavior management (PT) is a psychosocial intervention aimed at improving
120 caregiver's understanding of ADHD symptoms and helping them acquire skills to deal with
121 everyday challenging behavior and support child development. Although PT improves
122 parenting and reduces conduct problems, meta-analyses found no effect of PT on core ADHD
123 symptoms when raters were blinded to the treatment allocations(20). If, despite PT,
124 symptoms of ADHD persist and cause significant impairment of everyday functioning,
125 pharmacotherapy is recommended.

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3 126 Preferred medications include stimulants, which showed better efficacy (higher effect sizes)
4 127 on ADHD core symptom reduction and easier dose optimization protocols than non-
5 128 psychostimulating medications(21,22). Two psychostimulants with best evidence for
6 129 effectiveness and tolerability are methylphenidate (MPH) and lisdexamphetamine (LDX). LDX,
7 130 contrary to MPH, is an inactive prodrug that requires enzymatic conversion, resulting in an
8 131 extended and more stable acting time (~13h). In most international guidelines, LDX is advised
9 132 as first line treatment comparable to long-acting MPH, or as a secondary drug after treatment
10 133 failure with previous MPH medication attempts(22). In Poland LDX is neither reimbursed by
11 134 the National Health Fund (NHF) nor commercially available. As a result, long-acting MPH
12 135 formulations are considered the first-line pharmacotherapy for ADHD(23).

13 136 Limited retrospective data demonstrates that patients with ADHD and T1D treated with
14 137 stimulants show lower HbA1c ($8.1\pm 1.0\%$) compared to children that were diagnosed but not
15 138 treated pharmacologically ($8.5\pm 1.1\%$)(24). At the same time, others reported higher blood
16 139 pressure and no difference in metabolic control(12,13). However, generalization of those
17 140 results remains limited due to the low sample size, lack of evidence from RCTs, and no direct
18 141 comparisons between LDX and MPH. In conclusion, there is a lack of data on the safety and
19 142 effectiveness of ADHD medication in children with T1D regarding the effect on ADHD
20 143 symptoms, quality of life, and metabolic control.

21 144 **The aim of the Study**

22 145 The Trial aims to compare the safety and efficacy of ADHD treatment with LDX or MPH in
23 146 children and adolescents with ADHD and T1D.

24 147 **Methods and analysis**

25 148 **Study design and population**

26 149 LAMAI nDiab is a 2nd phase randomized cross-over open label clinical trial with blinded
27 150 endpoint assessment. Cross-over design was chosen based on the sample size analysis, as well
28 151 as for ethical reasons – to provide each participant with an active drug with proven efficacy in
29 152 ADHD. The project is funded by the Medical Research Agency (pol. “Agencja Badań
30 153 Medycznych”), which supports non-commercial clinical trials in Poland through open calls.
31 154 Upon grant application, the project consortium was established, and four recruiting sites –
32 155 that collectively provide care for ~25% of national pediatric population with T1D(25,26) – were
33 156 declared.

34 157 **Patient and Public Involvement statement**

35 158 The project was consulted with and was supported by a national patient organization (Polish
36 159 Federation for Support of Children and Adolescents with Diabetes, “Diabetycy.eu”), which
37 160 entered the project’s consortium. Clinical trial’s design and protocol were thoroughly
38 161 consulted with the organization, and its representative (MZ) was included among the authors
39 162 to acknowledge her input. Subsequently, the organization’s qualified representatives agreed
40 163 to play the roles of independent investigators blinded to the treatment allocation and perform
41 164 ADHD symptom assessments for participating children.

42 165 **Inclusion and exclusion criteria**

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3 166 Principal inclusion criteria:
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- 5 167 • Age 8-16.5 years at trial entry;
6 168 • T1D diagnosed according to National and International Guidelines(27)(28) at least 12
7 169 months before recruitment, treated with functional intensive insulin therapy,
8 170 • ADHD diagnosis according to 5th Edition Diagnostic and Statistical Manual of Mental
9 171 Disorders (DSM-5)(29) or International Statistical Classification of Diseases (ICD-10)(30)
10 172 and confirmed as consistent with DSM-5 by a psychiatrist;
11 173 • Polish citizenship and health insurance.

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15 174 Principal exclusion criteria:
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- 17 175 • Clinical partial remission of T1D (daily insulin dose<0.3 units per kilogram and concomitant
18 176 HbA1c measurement ≤6.5% from the last 3 months) or severely unsatisfactory glycemic
19 177 control (mean HbA1c over the past year ≥12%, excluding HbA1c measurement at T1D
20 178 diagnosis);
21 179 • Clinically apparent or previously-diagnosed cardiovascular disease: hemodynamically
22 180 significant heart defect, advanced vascular atherosclerosis, or documented hypertension
23 181 (at least stage 2);
24 182 • Diagnosed intellectual disability or other disability that prevents patient adherence to the
25 183 therapeutic regimen; history of other mental illness or disorder preventing participation
26 184 in the trial, e.g. bipolar disorder, schizophrenia, other psychotic disorders, history of
27 185 suicide attempts or present suicide intentions, psychoactive substances abuse;
28 186 • Contraindications (in line with product characteristics, described in detail at
29 187 <https://clinicaltrials.gov/study/NCT05957055>), allergy or hypersensitivity to either studied
30 188 drug.
31 189 • Language barrier making it impossible to conduct a full psychological consultation in
32 190 Polish, lack of permanent residence and national insurance in Poland;
33 191 • Declared inability or unwillingness of the parents/legal guardians' to come to the Centre
34 192 at the time specified by the protocol, in particular – to pick up the study drugs at the dose
35 193 adjustment stage (the need to pick up 4-5 times over 6-8 weeks, each time within 2-3 days
36 194 of receiving the recommendations);
37 195 • Other reasons that, in the opinion of the attending physician, are more likely to result in
38 196 difficulties in maintaining the participant's participation in the trial or harm to the
39 197 participant's health in case of participation in the trial.

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48 198 **Setting**
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50 199 The Trial will be conducted in 4 pediatric diabetology centres, and apply telemedical tools to
51 200 facilitate recruitment, improve compliance and reduce the burden on participants and their
52 201 families. The participating centres provide coordinated pediatric diabetes care for their
53 202 respective voivodeships (regions of Poland):

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56 203 • Lodzkie voivodeship: Department of Pediatrics, Diabetology, Endocrinology and
57 204 Nephrology, Pediatric Centre of the Central Clinical Hospital of the Medical University of
58 205 Lodz;
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3 206 • Silesian voivodeship: Department of Children's Diabetology, Medical University of Silesia,
4 207 Upper Silesian John Paul II Child Health Centre;
5
6 208 • Pomeranian voivodeship: Department of Pediatrics, Diabetology, and Endocrinology of the
7 209 Medical University of Gdansk, University Clinical Centre in Gdansk;
8
9 210 • Opole voivodeship: Department of Pediatrics of the Institute of Medical Sciences of the
10 211 University of Opole (Department of Pediatrics and the Diabetology Clinic for Children of
11 212 the University Clinical Hospital in Opole).

13 213 Information about the centres was published on the project's website - lamaindiab.umed.pl.
14 214 Pediatric diabetology centres included in the trial are public care providers – the trial visits and
15 215 procedures will be carried out as add-ons to routine visits related to the management of
16 216 diabetes. Pediatric healthcare in Poland is tax-financed by the National Health Found (NHF)
17 217 and provides universal, free-of-charge care for all children registered in Poland and their
18 218 caregivers.

21 219 **Summary of trial procedures**

22 220 Patients with ADHD and T1D, meeting the clinical trial's inclusion criteria may enroll into the
23 221 Trial in the designated reference centres. First, their guardians will receive information about
24 222 the study from the centre's representative via phone, followed by complete Information and
25 223 Consent forms sent to agreed mail address. During the next routine outpatient consultation,
26 224 the guardians and children will thoroughly discuss the information provided with an
27 225 investigator. After answering any questions related to the study and its protocol, the
28 226 investigator will verify inclusion and exclusion criteria and obtain signed informed consent
29 227 form in line with current regulations (from both parents and children $\geq 13y.o.$). After successful
30 228 recruitment, study procedures will be initiated. Simplified patient's course in the clinical trial
31 229 is demonstrated in Figure 1.

36 230 [FIGURE 1]

37 231 Each patient will begin the Trial starting with the enrollment appointment, followed by a
38 232 baseline assessment by a diabetologist and a psychological evaluation. At this stage, all trial
39 233 participants will be provided with the following devices: pre-configured tablets with
40 234 appropriate telecommunication software and prepaid internet access, wrist accelerometers,
41 235 and blood pressure monitors. All devices will be provided by the Medical University of Lodz to
42 236 assist participants and their parents in following the study procedures and data collection.
43 237 Additionally, willing patients who did not qualify for reimbursement will be provided with
44 238 continuous glucose monitoring (CGM) sensors and receivers and instructed in their use.

45 239 Next, the patient's parents/legal guardians will participate in a PT program of 10 themed
46 240 online workshops (once-weekly sessions, 90 minutes long) led by psychotherapists and
47 241 supplemented with homework and educational materials. PT aims to provide immediate
48 242 educational and behavioral support for the child's caretakers by educating them about ADHD
49 243 and providing tools and skills to understand and modify the child's behaviors and was
50 244 demonstrated to strengthen family bonds and improve adherence to future
51 245 pharmacotherapy. To successfully complete this part of the Trial, participant's guardians must
52 246 participate in at least 8 meetings – with a possible revisit of the missed ones in another cycle.

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3 247 After completion of PT, each participant will repeat the psychological evaluation to assess the
4 248 effects of PT intervention alone on ADHD symptoms severity. Those with sustained clinically-
5 249 significant ADHD symptoms will be qualified for pharmacological intervention. Possible
6 250 contraindications for pharmacotherapy will be assessed during the next diabetological visit.
7 251 The add-on procedures will include urine tests (pregnancy and panel test for substance use),
8 252 ECG with QT segment assessment (to exclude long QT syndrome) and ophthalmological
9 253 consultation (to exclude glaucoma). Subsequent and final assessment and qualification will be
10 254 performed by psychiatrist during an online consultation. Afterward, each participant starting
11 255 pharmacotherapy will be randomized using a digital randomization system to receive either
12 256 MPH or LDX as the first drug.

13 257 The dose titration protocol was based on Newcorn et al.(31) flexible-dose design
14 258 (NCT01552915), with modifications. The dose will be optimized during up to four biweekly
15 259 psychiatric consultations in a flexible manner (for 5-7 weeks, allowing both one-step increase
16 260 and decrease between set minimum and maximum dose for each studied drug). After the
17 261 maximum tolerated dose is established, patients will continue pharmacotherapy for 6 months.
18 262 During that time, treatment safety and efficacy will be evaluated twice - after first 3 months
19 263 by psychological and diabetes care team's evaluation (with small dose adjustments allowed)
20 264 and after full course (6 months) of therapy. On-demand psychiatric consultations will be
21 265 allowed. In addition, during both diabetological visits each participant will donate a dry blood
22 266 sample for evaluation of the concentration of an allocated drug, and another sample will be
23 267 self-collected on the day of the final psychological assessment for that arm to ensure that
24 268 endpoint measurements are not biased by incidental non-adherence. After the last
25 269 evaluation, participants will return the unused drug to their diabetes care centre and will begin
26 270 a wash-out period.

27 271 Qualification for the second arm of pharmacotherapy will be based on the same procedures
28 272 and consultations which will be performed in parallel with the last diabetological assessment
29 273 in the first arm. Final switch and start of the second drug (LDX or MPH) will be based on
30 274 psychiatrist decision. Dose adjustment, safety and efficacy monitoring will follow the same
31 275 procedures over the next 6 months. Schedule of the Trial's procedures was presented in
32 276 Supplementary Table 1.

33 277 At the end of patient's participation in the Trial, all the devices will be returned to the
34 278 University, and the last safety and efficacy interview will be performed. All the patients will
35 279 receive further treatment recommendations at NHF facilities.

36 280 **Randomization**

37 281 The starting drug will be determined using block randomization stratified by the trial centre in
38 282 a 1:1 ratio between MPH and LDX. The risk of randomization error will be minimized by using
39 283 a user-friendly "Randomizer" IT tool provided by the Sponsor, integrated with the eCRF. In the
40 284 event of unexpected randomization difficulties (e.g., lack of internet access or other technical
41 285 problems), centre's trial-coordinator may request randomization via backup randomization
42 286 list available only for sponsor's representative, re-randomization or patient's withdrawal.

43 287 **Blinding**

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3 288 The participant allocation is open both to the participant and their guardians as well as their
4 289 attending physician (diabetologist and psychiatrist alike). Blinding at participant level was
5 290 considered but decided against due to practical reasons (i.e. costs and difficulties in producing
6 291 effective over-encapsulation, high risk for spontaneous unblinding due to differences in
7 292 pharmacokinetics of the studied drugs). However, the people assessing the primary outcome
8 293 (i.e. ADHD symptom severity) will be blinded to the allocation and operating independently
9 294 from the care centres. No exceptions or unblinding options are planned for those researchers
10 295 as their assessment serves mostly research purpose, and data collected by them are reviewed
11 296 by unblinded clinicians.

15 297 **Endpoints and analysis**

16 298 The **primary endpoints** of the Trial are:

- 19 299 1. Efficacy, defined as change in the severity of ADHD symptoms ("inattention" and
20 300 "hyperactivity/impulsivity" measured by Conners 3 questionnaire) compared between
21 301 LDX vs. MPH.
- 23 302 2. Safety, defined as frequency of MedDRA-defined adverse events for both drugs.

24
25 303 For each participant, we will calculate the difference in questionnaire scores ("inattention"
26 304 and "hyperactivity/impulsivity") at the end of each arm versus the initiation of drug therapy
27 305 (before first drug). Separate comparisons will be made for each subscale and informant
28 306 (guardian/child).

29
30 307 Safety analysis will report the number of recorded events by type and severity and the
31 308 incidence rate (the number of events divided by the number of patient-months of
32 309 observation).

33
34
35 310 The **secondary endpoints** of the Trial are (all compared between LDX and MPH arms):

- 37 311 1. Diabetes control, as measured by HbA1c and CGM-derived time in target range, mean
38 312 sensor glucose, and coefficient of variation, before and after treatment with each of
39 313 investigated drugs;
- 41 314 2. General and diabetes-related quality of life (measured with PedsQL questionnaires),
42 315 before and after treatment with each of investigated drugs;
- 44 316 3. Number and percentage of trial participants that achieved improvement of ADHD
45 317 symptoms (Conners 3 "inattention" and "hyperactivity/impulsivity") defined as 33%
46 318 reduction in scale values compared to baseline.

47
48 319 The **exploratory endpoints** of the Trial are:

- 49
50 320 1. Difference between LDX vs. MPH in school attendance during the month preceding the 6-
51 321 month drug evaluation;
- 53 322 2. Difference between LDX vs. MPH in physical activity (daily steps, % of time in moderate-
54 323 to-vigorous physical activity) and sleep (duration, latency, efficiency) indices;
- 56 324 3. Differences between baseline assessment and after PT completion concerning: in ADHD
57 325 symptoms severity (Conners 3 "inattention" and "hyperactivity/impulsivity"), HbA1c and
58 326 CGM-derived glycemic control (time in range, mean sensor glucose, coefficient of
59 327 variation);

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3 328 4. Difference between LDX vs. MPH in frequency (number of events per patient-months) of
4 329 acute diabetes complications (severe hypoglycemia, ketoacidosis) and hospitalizations,
5 330 and number of days spent in inpatient care (number of days per patient-months).
6
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8 331 **Tools and parameters used during the Trial**

9
10 332 During in-patient visits in the Trial, standard procedures will be performed, including
11 333 anthropometric, heart rate, and blood pressure measurements. Applicable values will be
12 334 referenced with Polish percentile charts.

13
14 335 ADHD symptoms will be measured using The Conners' Rating Scales (The Conners 3.0 scales,
15 336 Polish version) completed by parents (Conners 3.0-P) and children (Conners 3.0-
16 337 SR). The Conners' Rating Scales are validated and most commonly used tools to assess
17 338 difficulties in children and adolescents with ADHD in research and clinical settings worldwide.
18 339 The Polish version of Conners 3.0 has proven high psychometric reliability and validity. In the
19 340 Trial, we will focus on changes in content scales of "Inattention" and
20 341 "Hyperactivity/Impulsivity", two core domains of ADHD symptoms by DSM-5(29).

21
22 342 Diabetes control will be assessed using HbA1c measured in local laboratories using methods
23 343 concordant with the NGSP program. Moreover, patients will be instructed to use continuous
24 344 glucose monitoring (CGM) according to their attending physicians' recommendations and
25 345 generated data will be collected during diabetes check-ups. In Poland, CGM is reimbursed in
26 346 the form of intermittently-scanned CGM, with possible extension into real-time CGM for those
27 347 with impaired awareness of hypoglycemia. If available, CGMs will be linked with appropriate
28 348 devices: insulin pumps, CGM readers, mobile phones. CGM data will be backed up and
29 349 processed using GlyCulator 3.0 platform(32). For wrist accelerometer data, manufacturer-
30 350 provided software will be used to collect the data for further analysis.

31
32 351 Patient's quality-of-life (QoL) will be measured using the Pediatric Quality of Life Inventory 3.2
33 352 Core (PedsQL QoL) and Diabetes Module (PedsQL diab)(33). The PedsQL is the most common
34 353 tool to measure QoL in the pediatric population. The PedsQL Diabetes Module allows focusing
35 354 on T1D-specific issues, especially relevant for the ADHD interaction with T1D self-control.
36 355 PedsQL QoL and diab have been translated into Polish and validated for academic and
37 356 commercial use.

38
39 357 During the drug dose-optimization period, patients will be tasked with performing self-
40 358 assessment, including self-monitoring of blood pressure using automated monitors, diabetes
41 359 monitoring with CGM, and activity monitoring using a wrist accelerometer. Blood pressure
42 360 monitors data will be periodically uploaded into a central data repository integrated with
43 361 electronic case report forms (eCRF), while wrist accelerometry will be stored and analysed at
44 362 the Trial completion. CGM data will be backed up on in-patient clinic visits using appropriate
45 363 software in each centre.

46 364 **Statistical analysis**

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48 365 The primary outcome will be compared between the LDX and MPH group using paired t-tests
49 366 and multivariable regression models to account for clinical covariates. Sensitivity analysis will
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367 be performed for primary and secondary endpoints for the subgroup of patients with no
368 imputed data.

369 For each intervention, the % of reported adverse events will be reported with the relevant
370 statistics for paired comparisons (Chi², p), and for the entire table (T_{MB}, p). The incidence rates
371 for individual adverse events will be compared with appropriate statistical tests (Poisson test
372 or equivalent). In addition, each type of event will be compared using the McNemar test, and
373 the frequencies of different events using the McNemar-Bowker global symmetry test.

374 Treatment safety will be assessed and reported following standard procedures and coded
375 using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and WHO severity
376 scale, and recorded in eCRF.

377 Safety and efficacy endpoints will be analysed using data from patients who completed both
378 planned treatments, independent of potential protocol deviations (i.e., population "as
379 treated"). Data of patients lost to follow-up will be filled in on the basis of last-observation
380 carried forward, provided that they have at least one complete timepoint of outcome
381 measures on the current treatment. Patients with deviations from protocol leading to no
382 outcome data will not be included in efficacy analyses.

383 The secondary and exploratory endpoints will be evaluated using the appropriate statistical
384 methods for either continuous (paired t-test, linear regression) or nominal variables
385 (McNemar test). Interim analyses were not planned within this study.

386 **Sample size estimation**

387 To our knowledge, at the time of planning this Trial, no trial with equivalent design and
388 outcome measures in this population was published. Thus, we calculated the sample size to
389 allow for detection of a moderate difference (0.33 standard deviations) difference in score
390 changes between LDX vs. MPH for the key Conners 3 measures(34). Such difference was
391 deemed clinically-impactful by the clinical team designing the trial. To estimate the sample
392 size, we assumed significance threshold of alpha=0.05, the statistical power of 80%. The risk
393 of applying multiple tests (each scale in each type of responder – four in total) was assessed
394 as minimal due to high intercorrelations among those measures. As such, no alpha adjustment
395 was planned. Such assumptions yielded the minimum number of participants of 89 (rounded
396 to 90). The risk of drop-out during pharmacotherapy was assessed as considerable (~33%) due
397 to the challenging population of interest (children with ADHD and T1D, with ADHD possibly
398 present in parents) and known side effects of tested medications. Thus, the target number of
399 pharmacologically-treated children was planned at 135, and 150 recruited given that up to
400 10% might be disqualified from pharmacotherapy due to drug contraindications or
401 considerable improvement after PT. Assuming recruitment success at 80% (considerable
402 benefit for patients, access to a drug unavailable in Poland, coordinated diabetes and
403 psychiatric care), we estimated that 190 children that should be approached. Based on the
404 general prevalence of ADHD in the pediatric population, the number of patients with T1D to
405 screen for ADHD would be at least 4000 – which was a number of patients supervised by the
406 4 Trial centres.

407 **Data entry and storage**

408 Patient data collected during the clinical Trial will be stored within the electronic trial
409 documentation database, following appropriate regulations, with data access provided to
410 appropriate trial personnel. Reported, presented, and published data will be anonymized. The
411 clinical trial records will be stored for 25 years after trial completion.

412 **Trial monitoring**

413 Trial monitoring will follow adequate international and national clinical trial regulations.
414 Sponsor's representatives will visit each site, discuss the clinical trial course, review and
415 validate relevant records, and verify all reference centres' that partake in the clinical trial.
416 National regulatory authorities may request access to research documentation, source
417 documents, research personnel, and facilities. The Sponsor will be notified of any centre's
418 audits by regulatory agencies, and copies of audit reports will be transferred accordingly.

419 **Trial timeline**

420 Planned date for starting the study is 1.01.2024, but may be prone to change following logistic
421 reasons. The trial is planned to last 48 months, setting the tentative end date of the study at
422 1.12.2027.

423

424 **Ethics and dissemination**

425 **Ethical considerations**

426 The clinical trial follows principles of the Helsinki Declaration, current Good Clinical Practice
427 guidelines, and other applicable regulations. The clinical trial has been registered in European
428 Union Drug Regulating Authorities Clinical Trials Database (no. 2022-001906-24) and in
429 ClinicalTrials.gov (NCT05957055). The clinical trial was approved by the Bioethical Committee
430 at Medical University of Lodz (agreement no. RNN/142/22/KE), and the Polish Office for
431 Registration of Medicinal Products, Medical Devices and Biocidal Products
432 (UR/DBL/D/263/2022). All participants of the clinical trial are insured within the appropriate
433 insurance agreements (policy no. COR233280) and signed informed consent forms from them
434 and their parents will be collected before trial procedures. All changes in the Trial are subject
435 to ethical and regulatory review before their incorporation into the clinical trial.

436 **Safety during and post intervention**

437 Before the intervention, the treatment of coexisting diseases will be recorded in the eCRF and
438 continued as is or appropriately modified by the respective specialist. All adverse events will
439 be documented in the electronic trial documentation using MedDRA v24.1 and graded using
440 applicable WHO standards, with SAE reported within 24 hours since the occurrence and
441 evaluated by Safety Monitoring Team (SMT). In case of a SUSAR, the SMT follows the Council
442 for International Organizations of Medical Sciences forms and reports it to appropriate
443 authorities within 15 days (or 7 in case of threat to the life or death of the patient) from
444 receiving the report, following the data transfer procedure with the applicable law. The SMT
445 will provide an annual patient safety report throughout the clinical trial, including appropriate

446 information on treatment safety. The Sponsor holds the right to pause or discontinue part of
447 the trial, the entire trial, or the participation of an individual patient.

448 After trial completion, all the patients will receive further treatment instructions, prescription
449 for ADHD treatment and referral to appropriate health provider facilities. Reference
450 diabetology centres will provide continued diabetes care under NHF.

451 **Dissemination plan**

452 Results will be submitted for publication in leading international scientific journals in diabetes
453 care, endocrinology and psychiatry. Results will also be shared during relevant national and
454 international congresses and conferences. The cooperation between the Sponsor and patient
455 organization (affiliation 13) will be continued after the Trial's completion to increase
456 awareness of the impact of psychiatric diseases in patients with T1D. The study's results will
457 also be communicated to the funding agency and national healthcare policy makers.

458 **Discussion**

459 Despite the favorable opinion of the Polish Agency for Health Technology Assessment and
460 Tariff System, LDX is still unavailable for Polish patients outside this clinical trial. We will
461 provide data collected during this Trial for consideration of the Agency, to promote discussion
462 about the availability of LDX and advocate for it being widely accessible (if not reimbursed).
463 We will also perform a specific cost-effectiveness analysis for the particular population of
464 children with ADHD and T1D, and investigate possible costs and benefits of considering LDX
465 as a first-line treatment in this group of patients, justified by the system savings provided by
466 possibly-improved diabetes control.

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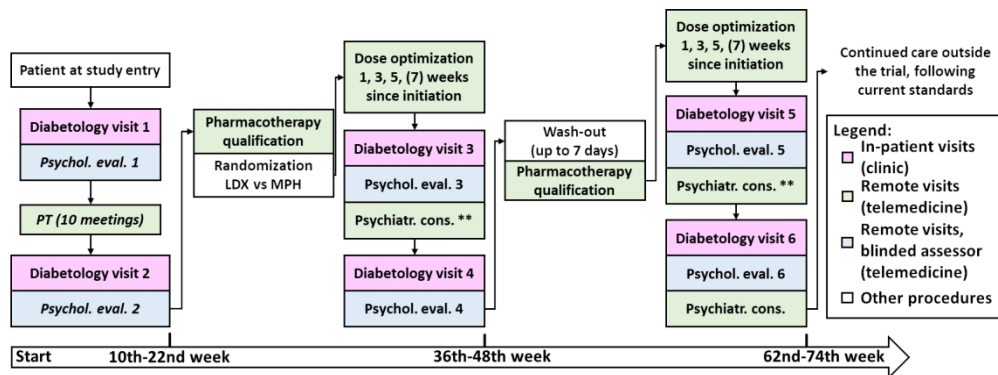
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56 607 **Author contribution:** AM, JC, HKK, WF, AB, KB – written the article, prepared the clinical
57 608 trial protocol; WF, AB, AM, KB – supervised the clinical trial registration; EK – translated the
58 609 clinical trial protocol and written the supplementary materials; BM, ASz, ACh, PJCh, MM, IM,
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3 610 AK, TW, WF, AB – consulted the manuscript and the clinical trial protocol; MZ –supervised
4 611 patients consultation of the clinical trial. All authors reviewed the results and approved
5
6 612 the final version of the manuscript. We comply to the ICMJE guidelines.
7

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14 618 study is a non-commercial clinical trial funded by the Polish Medical Research Agency.
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18 619 **Figure 1.** Simplified study design flowchart. PT – parental training, LDX – lisdexamphetamine,
19 620 MPH – methylphenidate. ** - if needed on-demand consultation
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19 Figure 1. Simplified study design flowchart. PT – parental training, LDX – lisdexamphetamine, MPH –
20 methylphenidate. ** - if needed on-demand consultation

21 315x117mm (150 x 150 DPI)

1 **Supplementary Table 1.** Study schedule. The order of treatment (A/B) will be decided at randomization (allocation step). Names of visits corresponding to
 2 Figure 1 are included.

		STUDY PERIOD								
		Enroll	PT	Allocate	Post-allocation					
DURATION		1 week	10-22 weeks	1 week	First treatment (6 months)			Second treatment (6 months)		
ENROLLMENT	Eligibility screen	X		X			X			
	Informed consent	X								
	Randomization (to A/B)			X						
INTERVENTION	Parent training in behaviour management		X							
	Cross-over	MPH			A	A	A	B	B	B
		LDX				B	B	B	A	A
ASSESSMENTS	Conners 3, PedsQL questionnaires	Psychological evaluation 1		Psychological evaluation 2		Psychological evaluation 3	Psychological evaluation 4		Psychological evaluation 5	Psychological evaluation 6
	Diabetes control (HbA1c, CGM)	Diabetological visit 1		Diabetological visit 2		Diabetological visit 3	Diabetological visit 4		Diabetological visit 5	Diabetological visit 6
	Anthropometric, BP, HR measurement									
	Urine tests, ECG with QT segment assessment, ophthalmologic consultation									
	Psychiatric consultation			LDX/MPH qualification	Dose optimization	*Additional dose adjustment		Dose optimization	*Additional dose adjustment	Referral to care under National Health Fund

3 *optional, up to the Investigator, only lowering of dose allowed



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Line
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	S2: 5-8 S2: 10
	2b	All items from the World Health Organization Trial Registration Data Set	S2: 4-150
Protocol version	3	Date and version identifier	S2: 3
Funding	4	Sources and types of financial, material, and other support	569-570
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5-8 563-568
	5b	Name and contact information for the trial sponsor	S2: 14 S2: 16-19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	151-156 229-232 271-272 277-281 570-571 S2: 152-166
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the Trial, if applicable (see Item 21a for data monitoring committee)	S2: 167-201
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the Trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	87-144 S1: 58-121 S1: 299-410 S1: 637-673 S1: 885-897 S1: 944-983
	6b	Explanation for choice of comparators	323-355
Objectives	7	Specific objectives or hypotheses	145-148 289-322
Trial design	8	Description of trial design including type of Trial (eg, parallel group, cross-over, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	151-152 250-252 S2: 98-99
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	195-215
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	167-196
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	216-273 S2: 28-32
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	166-194 253-269 433-434 S2: 311-382 S2: 515-517 S2: 752-757
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	258-263 441-443 S2: 142-147
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the Trial	424-425
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	289-355 S2: 103-142

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and wash-outs), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 Table 1 224-273
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	378-398 S2: 101
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	151-156 158-164 196-226 387-398
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	274-281
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	274-281
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	274-281
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	282-288 S2: 28-32 S2: 103-142 S2: 179-182
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the Trial	282-288
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	289-323 323-355 S2: 122-298 S2: 420-431 S2: 438-458 S2: 674-884 S2: 983-1195
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	237-242 369-374
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	399-403 S2: 174-150 S2: 183-188
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	356-377
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	356-377
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	369-374
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	S2: 167-201
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the Trial	423-434
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	425-434
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	404-410
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	416-418 S2: 143-144

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	420-422
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	218-225 S1: 509-537 S1: 1226-1259
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	218-225 S1: 412-419 S1: 476-484 S1: 898-903 S1: 1214-1221
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the Trial	286-288 334-355 366-368 399-403 424-433 S1: 491-503 S1: 538-600 S1: 892-897 S1: 1261-1322 S2: 147-150
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall Trial and each study site	571
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	405-410 424-433 S2: 183-188
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	438-443 S1: 223-225
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	437-442 S1: 51-57 S1: 380-382 S1: 470-475 S1: 1209-1213
	31b	Authorship eligibility guidelines and any intended use of professional writers	564-569
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	439-443 S1: 491-503 S1: 538-600 S1: 892-897 S1: 1261-1322
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	S1: 30-601 S1: 616-906 S1: 922-1322
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current Trial and for future use in ancillary studies, if applicable	S1: 412-419 S1: 476-484 S1: 898-903 S1: 1214-1221

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.