PROJECT FINAL REPORT

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Project acronym: MID-FRAIL-STUDY

Project title: ***A randomised clinical trial to evaluate the effectiveness of a multi-modal intervention in frail and pre-frail older people with type 2 diabetes: The MID-Frail study***

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Content

1. Executive summary.

Diabetes is a high prevalence disorder in ageing populations (20% in people ≥ 65 yrs) with a chronic disease time-course and is associated with considerable medical co-morbidity, functional loss and frailty, visual and lower limb disability, multiple medication usage and impaired quality of life and results in a high personal and social health burden, and a significant public health burden.

Diabetes is associated with increased frailty and functional decline in older people and may explain up to 20% of the excess risk of disability in an elderly population, with an annual relative risk of developing any disability around 2.0.

The MID-FRAIL-STUDY project focuses on the use of interventions designed to improve functional status and enhance quality of life rather than traditional treatments such as glucose- and blood pressure- lowering by acting on the mechanisms involved in producing frailty and its progression to adverse outcomes.

The main objective is to evaluate, in comparison with usual clinical practice, the effectiveness of a multi-modal intervention (education, diet and exercise) in frail and pre-frail subjects aged ≥ 70 years with T2D in terms of the difference in function 12 months post randomization, according to changes in score on the SPPB.

As secondary objectives, to evaluate the effect on economic health care costs, symptomatic hypoglycaemia, hospital admissions, permanent institutionalization and carer burden.

Nine hundred and sixty four subjects were included in 74 trial sites along 9 European countries. Baseline characteristics were comparable between both groups (intervention and usual care group).The mean age was 78 years (SD 5.44), and 50.9% were men and 37,7% were fragile.

Regarding the main variable, changes in function after 12 months of follow up measured by SPPB test, the intervention group showed a statistically significant improvement in the SPPB score respect the usual care group.

The results of this preliminary analysis show that the MID-FRAIL intervention induced significant improvement of QoL in older patients with diabetes. Especially the ADDQoL-Senior was sensitive for detecting differences between changes in QoL after 1 year between intervention and control. EQ5D scores were significantly related to the item ‘general health’ of the ADDQoL-Senior, which can be explained by the rather generic QoL domains measured with EQ5D.

The economic evaluation shows that, regardless of the chosen health indicator (SPPB score, percentage of patients with improvement in SPPB score ≥ one point or QALYs), the intervention dominates usual care. That is, the intervention program achieves better health outcomes at the same or lower cost than usual care. Therefore, the intervention program is efficient compared to usual care. The sensitivity analyses performed show that the results are consistent and the conclusions are robust, independently of the changes performed in the parameters and in the variables considered.

2. Summary description of project context and objectives

1. Background

Diabetes is a high prevalent metabolic disorder in ageing populations and is associated with considerable medical co-morbidity, functional loss and frailty, visual and lower limb disability, multiple medication usage and impaired quality of life. The impact on the individual is thus high and the impact on society is costly in terms of increased hospitalisation, community and primary care health and social care costs, and increased care home residency.

Older patients with diabetes have an increased risk of disabling complications associated with lower limb dysfunction and increased falls risk. The MIDFrail Study is a timely innovative and unique study that addresses real clinical issues such as the prevention of disability by its focus on frailty, a pre-disability state. The interventions used (resistance training, nutritional and diabetes education and medical treatment optimisation) provide a novel approach to minimising the progression of pre-frail and frail states to disability and as such as high potential for demonstrating cost-effective interventions in our ageing society.

The MID-FRAIL-STUDY is an innovative clinical trial that may produce the first objective evidence the utility of a multimodal intervention in ageing subjects with type 2 diabetes and features of frailty. The focus of the study is centred around clinical outcomes measured by functional assessment and an enquiry into quality of life dimensions.

The information derived from the MIDFrail Study will enrich the evidence base for studies in diabetic subjects of advanced age, provide meaningful messages about what type of interventions are suitable for older people to undertake with a high degree of confidence and safety, and lead to recommendations in diabetes guidelines that can be implemented widely across the EU and globe.

A number of key benefits to the health status and well-being of European ageing citizens is expected if the anticipated findings the MIDFrail Study are implemented across the European Union: these are related to significant numbers of older people with diabetes which we have previously calculated to be equivalent to nearly 700,000 fewer cases of disability per year in the EU. A consequence of the reduction in disability levels will be huge savings in social and healthcare expenditure which we have previously calculated to 3 billion euros per year, thus enabling the opportunity to re-invest some of these savings into more sustainable integrated healthcare systems for older people in general and in those with diabetes in particular. We anticipate a greater opportunity to establish networks of support across the EU of groups that have a significant interest in gerontological research who will want to work with the present consortium to develop new initiatives in the area of ageing, frailty and diabetes.

The MIDFrail study is the first of its kind in the world that has targeted a vulnerable and often neglected group of patients and as such the data will be unique and original. It has already brought together a consortium of academics, SMEs and not for profit research organisations, clinical scientists, pharmacologists and health economists that have a major interest in the applied research of older people which provides a tremendous platform for other future EU-wide research initiatives.

2. Objectives:

Main objective:

To evaluate the effectiveness of a multi-modal intervention in frail and pre-frail subjects aged 70 years with T2D in terms of function and quality of life in comparison with usual clinical practice after 12 months post randomization.

Secondary objectives:

To evaluate, in comparison with usual clinical practice, the effectiveness of a multi-modal intervention in any of the following:

(1) Economic costs/healthcare expenditure due to diabetes;

(2) Incidence rate of symptomatic hypoglycemia and hypoglycemic coma;

(3) Incidence of hospital admission;

(4) Incidence of permanent institutionalization, and

(5) Carer burden.

3. Substudies

To evaluate the mechanisms underlying the effects of the intervention:

- Studying the changes in the body composition with exercise (**SARTRAIN SubStudy**)
- Studying the effect of increased power in both isometric and dynamic actions (**MID-POW SubStudy**);
- Studying the role of metabolome (**MetaboFrail SubStudy**)
- Studying tha genetic polymorphisms (**GeneFrail SubStudy**) as determinants of the response to treatment.
- To evaluate the efficacy of new therapeutic devices (**SENSOLE SubStudy**)
- To evaluate new ways to measure changes in QoL (**QoLFrail SubStudy**).

4. Design

This is an open-label cluster randomized multicentre superiority trial, with random allocation by clusters (Trial sites-TS) to a Usual Care Group (UCG) or an Intervention Group (IG). Simple cluster randomization using blocks of size [redacted], stratified by country

The original sample size was based on a dichotomous change in SPPB score of one or more points and resulted in a sample size of 1,718. We since changed the way the primary outcome is measured to use the continuous version of the SPPB and look for a difference between groups of 1 point on average. The new target sample size is 1000 patients. Under the initial assumptions regarding attrition (20%), clustering resulting in a design effect of 1.746875 (an intra cluster coefficient of 0.05, an average cluster size of 15 and a coefficient of variation of cluster size of 0.25 (CONSORT GROUP 2014 and ELDRIDGE), a standard 5% significance threshold (alpha), a two-sided test, we have 97% power to detect a mean difference of one SPPB point between the two groups as statistically significant (nQuery v7.0).

The original study was intended to follow all participants up until 2 years however this was amended to one year in order to extend recruitment.

5. Inclusion and exclusion criteria

The subject can enter the study if ALL of the following apply*:*

- Subject is willing and able to give written informed consent for participation in the study.
- Subject is aged 70 years or older, with a diagnosis of T2D for at least 2 years.
- Require to fulfil Fried´s criteria for frail or pre-frail individuals.

The subject cannot enter the study if ANY of the following apply*:*

- Barthel score lower than 60 points.
- Inability to carry out SPPB test (total score=0).
- Mini Mental State Examination score less than 20 points.
- Subjects unwilling or unable to consent or unable to participate safely in intervention program.
- Previous history of myocardial infarction within 6 months, unstable angina or congestive heart failure in III-IV NYHA stage.
- Clinically instable patients in the clinical judgment of the investigator.
- Terminal illness (life expectancy < 6 months).
- Any other condition that, in the clinical judgment of the investigator, means that it would not be in the best interests of the subject to enter the study.
- Current participation in a clinical trial or any other investigational study.

6. Procedures during the study

(figure 1)

Visit	Screening	Baseline W0	Visit 1 W10 (+/- 1 W)	Visit 2 W18 (+/- 2W)	Visit 3 W26 (+/- 2W)	Visit 4 W52 (+/- 3W)	Visit 5 W 60 (+/- 3W)	Visit 6 W 68 (+/- 3W)	Visit 7 W78 (+/- 4W)	Visit 8 W104 (+/- 4W)
Medical History	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Demographics	X									
Physical Examination	X		X	X	X	X	X	X	X	X
HR and BP	X		X	X	X	X	X	X	X	X
Plasma glucose	X		X	X	X	X	X	X	X	X
Full blood count	X									
Creatinine	X				X	X			X	X
HbA1c	X		X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Functional Assessment										
SPPB	X	X	X	X	X	X	X	X	X	X
MMSE	X									
IADL (Lawton)		X	X	X	X	X	X	X	X	X
Barthel Index	X	X	X	X	X	X	X	X	X	X
Assessment for Fried´s Criteria	X					X				X
Economic resource use for patients		X			X	X			X	X
Episodes of Hypoglycaemia		X	X	X	X	X	X	X	X	X
Permannt Institutionalization					X	X			X	X
Episodes of					X	X			X	X
EQ 5D-5L		X			X	X			X	X
ADDQoL-Senior		X			X	X			X	X
Modified Caregiver Strain Index		X			X	X			X	X
EQ 5D 5L for carers		X			X	X			X	X
Economic resource use for carers		X			X	X				X

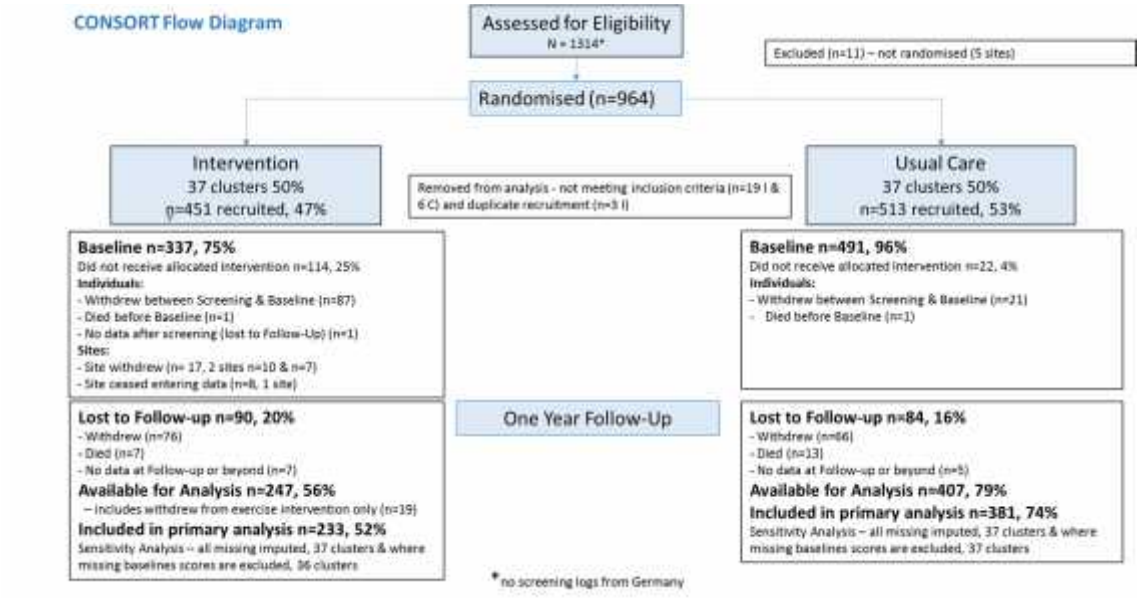
Data for this study was collected in sites on paper and then uploaded locally via an online data system provided by OnMedic and site based and central data monitoring and querying was undertaking by Niche, with further data cleaning undertaken in Cardiff prior to database lock. This was detailed in the trial protocol and data management plan and included

3. Description of the main S&T results/foregrounds

As the data obtained are very sensitive and are subject to restrictions of the scientific journals, only preliminary results will be submitted in this report. We will inform to EC about these definitive results in other separate document when these are available.

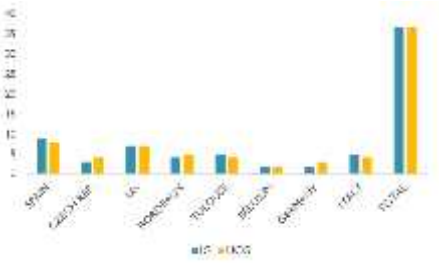
1. Participants

The flowchart with subjects included in the study and in the analysis is showed in the following figure. (figure 2)



Ninety six sites were involved in the study and 74 sites were randomized. The following table and figure show the number of trial sites included by country allocated to each arm: (figure 3)

COUNTRY/ARM	IG	UCG
SPAIN	9	8
CZECH REP.	3	4
UK	7	7
BORDEAUX	4	5
TULOUSE	5	4
BELGIUM	2	2
GERMANY	2	3
ITALY	5	4
TOTAL	37	37



2. Baseline characteristics

The main baseline characteristics per country of subjects included in the study are showed in the next table. There were some variations between countries in terms of the demographic nature of the sample recruited, particularly by gender. (Figure 4)

Baseline demographics by country. (figure 4)

	Belgium N=40 No. Sites = 4	Czech Republic N=96 No. Sites = 7	France N=226 No. Sites = 18	Germany N=80 No. Sites = 5	Italy N-126 No. Sites = 9	Spain N=226 No. Sites = 16	UK N=130 No. Sites = 14	**Total N=964** No. Sites = 73
Male - n (%)	21 (52.5)	25 (26.0)	133 (58.8)	39 (48.8)	87 (69.0)	103 (38.7)	83 (63.8)	491 (50.9)
Age – Mean (SD)	76.5 (5.37)	76.2 (6.30)	78.2 (5.44)	79.0 (5.95)	77.1 (4.64)	79.1 (5.24)	77.2 (4.98)	78.0 (5.44)
Number of years in education - Mean (SD)	14.3 (3.6)	13.2 (2.8)	10.2 (4.1)	11.0 (3.3)	8.8 (5.0)	7.5 (5.3)	11.4 (3.5)	10.0 (4.8)
Weight – Mean (SD)	82.9 (18.75)	79.4 (16.51)	81.3 (15.20)	79.8 (17.08)	78.0 (13.32)	71.9 (12.86)	85.7 (14.61)	78.6 (15.43)
Height – Mean (SD)	1.6 (0.08)	1.6 (0.09)	1.6 (0.09)	1.7 (0.09)	1.6 (0.09)	1.6 (0.08)	1.7 (0.10)	1.6 (0.10)
BMI – Mean (SD)	30.6 (5.32)	29.3 (5.47)	30.1 (5.22)	29.0 (5.74)	28.7 (4.34)	29.2 (4.50)	30.5 (4.72)	29.6 (4.96)
Frail - n (%)	18 (45.0)	38 (39.6)	69 (30.5)	26 (32.5)	31 (24.6)	122 (45.9)	60 (46.2)	364 (37.8)
Race - n (%) White Caucasian Latino Hispanic Other	 40 (100)	 96 (100)	 224 (99.1) 0 2 (0.9)	 78 (97.5) 0 2 (2.5)	 125 (99.2) 0 1 (0.8)	 200 (75.2) 61 (22.9) 5 (1.9)	 119 (91.5) 0 11 (8.5)	 882 (91.5) 61 (6.3) 21 (2.1)
Previous symptomatic hypoglycaemia - n (%)	8 (29.6)	4 (4.3)	33 (15.6)	16 (24.6)	7 (7.3)	16 (7.0)	6 (4.8)	90 (10.7)
Age at diagnosis - Mean (SD)	58.4 (8.7)	64.0 (12.2)	59.7 (16.6)	62.8 (11.7)	59.7 (13.5)	60.8 (18.0)	62.2 (10.4)	61.0 (15.1)
Years since diagnosis – Mean (SD)	17.8 (9.46)	12.2 (10.56)	18.2 (16.37)	16.2 (10.19)	17.8 (13.68)	18.2 (16.97)	14.7 (9.70)	16.9 (14.49)
Heart rate – Mean (SD)	69.5 (12.38)	74.1 (9.80)	72.0 (10.67)	74.0 (11.33)	72.4 (11.27)	75.3 (11.29)	72.4 (11.60)	73.3 (11.17)
Systolic blood pressure – Mean (SD)	142.6 (19.52)	141.5 (13.09)	141.9 (19.96)	146.5 (23.68)	136.6 (18.15)	138.9 (17.75)	136.5 (17.48)	140.0 (18.71)
Diastolic blood pressure – Mean (SD)	75.7 (14.33)	78.7 (10.82)	75.7 (11.63)	78.3 (12.15)	75.9 (10.02)	74.4 (10.17)	71.3 (11.35)	75.3 (11.25)

Comorbidities – n (%)								
Hypertension	36 (90.0)	86 (89.6)	193 (85.4)	71 (88.8)	115 (91.3)	230 (86.5)	107 (82.3)	838 (86.9)
Stroke/TIA	5 (12.5)	12 (12.5)	34 (15.0)	15 (18.8)	19 (15.1)	32 (12.0)	15 (11.5)	132 (13.7)
Cancer	5 (12.5)	13 9(3.5)	38 (16.8)	20 (25.0)	16 (12.7)	26 (9.8)	9 (6.9)	127 (13.2)
Hip fracture	3 (7.5)	5 (5.2)	5 (2.2)	4 (5.0)	2 (1.6)	13 (4.9)	4 (3.1)	36 (3.7)
Osteoporosis	9 (22.5)	19 (19.8)	11 (4.9)	13 (16.3)	18 (14.3)	62 (23.3)	7 (5.4)	139 (14.4)
Parkinson’s Disease	1 (2.5)	2 (2.1)	3 (1.3)	1 (1.3)	2 (1.6)	16 (6.0)	5 (3.8)	30 (3.1)
Asthma/COPD	6 (15.0)	9 (9.4)	29 (12.8)	12 (15.0)	17 (13.5)	42 (15.8)	21 (16.2)	136 (14.1)
CHF	4 (10.0)	8 (8.3)	8 (3.5)	18 (22.5)	10 (7.9)	29 (10.9)	5 (3.8)	82 (8.5)
OA/RA	8 (20.0)	38 (39.6)	43 (19.0)	17 (21.3)	38 (30.2)	84 (31.6)	39 (30.0)	267 (27.7)

The next table shows the main baseline characteristics in each arm of the study. The two randomised groups where broadly similar demographically and on baseline measures of the outcomes.

Baseline demographics by Trial arm (figure 5)

	Intervention N= 451	**Usual Care** N = 513	**Total** N = 964
Male n (%)	222 (49.2)	269 (52.4)	491 (50.9)
Age – Mean (SD) [N]	78.4 (5.58) [451]	77.6 (5.29) [513]	78.0 (5.44) [964]
Number of years in education Mean (SD) [N]	9.5 (4.44) [448]	10.4 (5.00) [508]	10.0 (4.76) [956]
Weight – Mean (SD) [N]	77.6 (14.95) [450]	79.5 (15.79) [513]	78.6 (15.43) [963]
Height – Mean (SD) [N]	1.6 (0.10) [447]	1.6 (0.10) [506]	1.6 (0.10) [953]
BMI – Mean (SD) [N]	29.3 (4.96) [447]	29.8 (4.96) [506]	29.6 (4.96) [953]
Frail n (%)	170 (33.1)	194 (43.0)	364 (37.8)
Race n (%)			
White Caucasian	482 (94.0)	400 (88.7)	882 (91.5)
Latino Hispanic	15 (2.9)	46 (10.2)	61 (6.3)
Other	16 (3.2)	5 (1.1)	21 (2.1)
Previous symptomatic hypoglycaemia? Yes n (%)	40 (11.4)	50 (10.2)	90 (10.7)
Age at diagnosis Mean (SD) [N]	62.9 (12.97) [330]	59.6 (16.26) [474]	61.0 (15.07) [804]
Years since diagnosis – Mean (SD) [N]	15.1 (12.15) [330]	18.1 (15.83) [474]	16.9 (14.49) [804]
Heart rate – Mean (SD) [N]	73.2 (11.04) [448]	73.4 (11.29) [511]	73.3 (11.17) [959]
Systolic blood pressure – Mean (SD) [N]	140.6 (18.37) [447]	139.5 (19.00) [509]	140.0 (18.71) [956]
Diastolic blood pressure – Mean (SD) [N]	74.6 (10.09) [447]	75.9 (12.15) [509]	75.3 (11.25) [956]
Comorbidities – n (%)	385 (85.4)	453 (88.3)	838 (86.9)
Hypertension	55 (12.2)	77 (15.0)	132 (13.7)
Stroke/TIA	49 (10.9)	78 (15.2)	127 (13.2)
Cancer	16 (3.5)	20 (3.9)	36 (3.7)
Hip fracture	67 (14.9)	72 (14.0)	139 (14.4)
Osteoporosis			
Parkinson's Disease	15 (3.3)	15 (2.9)	30 (3.1)
Asthma/COPD	56 (12.4)	80 (15.6)	136 (14.1)
CHF	41 (9.1)	41 (8.0)	82 (8.5)
OA/RA	140 (31.0)	127 (24.8)	267 (27.7)

The next table shows the baseline functional measures by Trial arm (figure 6)

	Intervention N= 451	**Usual Care** N = 513	**Total** N = 964
SPPB	8.2 (2.61) [353]	8.6 (2.65) [491]	8.4 (2.64) [844]
Barthel	96.3 (7.03) [353]	95.7 (7.57) [491]	96.0 (7.35) [844]
IADL	7.1 (1.53) [353]	6.8 (1.76) [491]	6.9 (1.67) [844]
EQ-5D-5L	0.8 (0.20) [350]	0.8 (0.23) [489]	0.8 (0.22) [839]
MMSE	26.9 (2.96) [451]	26.9 (3.18) [513]	26.9 (3.08) [964]
MCSS	22.3 (8.33) [20]	20.0 (4.94) [32]	20.9 (6.47) [52]

Next table shows the baseline medications by trial arm. (figure 7)

	Intervention	Usual Care	**Total**
Antibiotic/antiinfectives – n (%)	35 (7.8)	62 (12.1)	97 (10.1)
Anticoagulant – n (%)	63 (14.0)	98 (19.1)	161 (16.7)
Antiglycaemic agent – n (%)	330 (73.8)	403 (78.6)	733 (76.0)
Anti-hypertensive (including ACE inhibitor) - n (%)	393 (87.1)	449 (87.5)	842 (87.3)
Central Nervous system drug (e.g., hypnotic, antidepressant) - n (%)	150 (33.3)	194 (37.8)	344 (35.7)
Gastro-intestinal drug - n (%)	183 (40.6)	209 (40.7)	392 (40.7)
Insulin - n (%)	144 (31.9)	210 (40.9)	354 (36.7)
Lipid-lowering agent - n (%)	272 (60.3)	303 (59.1)	575 (59.6)
NSAID - n (%)	225 (49.9)	259 (50.5)	484 (50.2)
Over-the-counter - n (%)	144 (31.9)	231 (45.0)	375 (38.9)
Other drug - n (%)	235 (52.1)	277 (54.0)	512 (53.1)
Other cardiovascular drug - n (%)	108 (23.9)	137 (26.7)	245 (25.4)
Other painkiller - n (%)	106 (23.5)	153 (29.8)	259 (26.9)
Respiratory Drug (including inhaler) - n (%)	42 (9.3)	62 (12.1)	104 (10.8)

Retention of participants has been a major challenge during the study. Withdrawals have exceeded 20%, most of them before the initiation of intervention. Therefore, we have analysed the baseline characteristics between those who had data at follow-up to one year and those who didn't. Next table provides this comparison. The major difference was that participants in intervention clusters were far more likely to be lost to follow-up. The second factor which was those who were frail at baseline were less likely to be followed at one year. The potentially biases arising from these will be considered in the sensitivity analysis of the primary outcome.

(figure8)

		Without (n=350)		With (n=614)	
		n	%	n	%
Gender of participant	Female	172	49.1	301	49.0
Age of participant (Median (IQR))		350	79 (74, 82)	614	77 (73, 81)
Treatment allocation	Intervention	218	62.3	233	37.9
Fried's Frailty Criteria	Frail	164	46.9	200	32.6
Country	Belgium	28	8.0	12	2.0
	Czech Republic	16	4.6	80	13.0
	France	62	17.7	164	26.7
	Germany	40	11.4	40	6.5
	Italy	42	12.0	84	13.7
	Spain	93	26.6	173	28.2
	UK	69	19.7	61	9.9
Previous symptomatic hypoglycaemia	Yes	28	12.1	62	10.1
What age were you diagnosed with diabetes (Median (IQR))		205	65 (56, 70)	599	63 (55, 70)
Number of years in education Mean (Median (IQR))		343	10 (6.5, 12)	613	10 (7, 13)
Hypertension	Yes	306	87.4	532	86.6
Stroke/TIA	Yes	57	16.3	75	12.2
Cancer	Yes	44	12.6	83	13.5
Hip fracture	Yes	15	4.3	21	3.4
Osteoporosis	Yes	56	16.0	83	13.5
Parkinson's Disease	Yes	10	2.9	20	3.3
Asthma/COPD	Yes	59	16.9	77	12.5
CHF	Yes	44	12.6	38	6.2
OA/RA	Yes	107	30.6	160	26.1
Baseline SPPB (Median (IQR))		230	8 (6, 10)	614	9 (7, 11)
Baseline IADL (Median (IQR))		232	8 (6, 8)	614	8 (6, 8)
Baseline Barthel (Median (IQR))		90	100 (95, 100)	183	100 (95, 100)
Baseline ADDQoL (Median (IQR))		223	0.00 (-0.24, 0.27)	608	0.00 (-0.35, 0.12)

3. MID Frail main analysis

The analysis of SPPB test shows that the intervention arm had SPPB scores on average about 5/6ths of an SPPB point higher (indicating better function) than the control arm at one year follow-up (95% CI: 0.44, 1.26, p-value <0.001).

The compliance of the intervention resulted 80%.

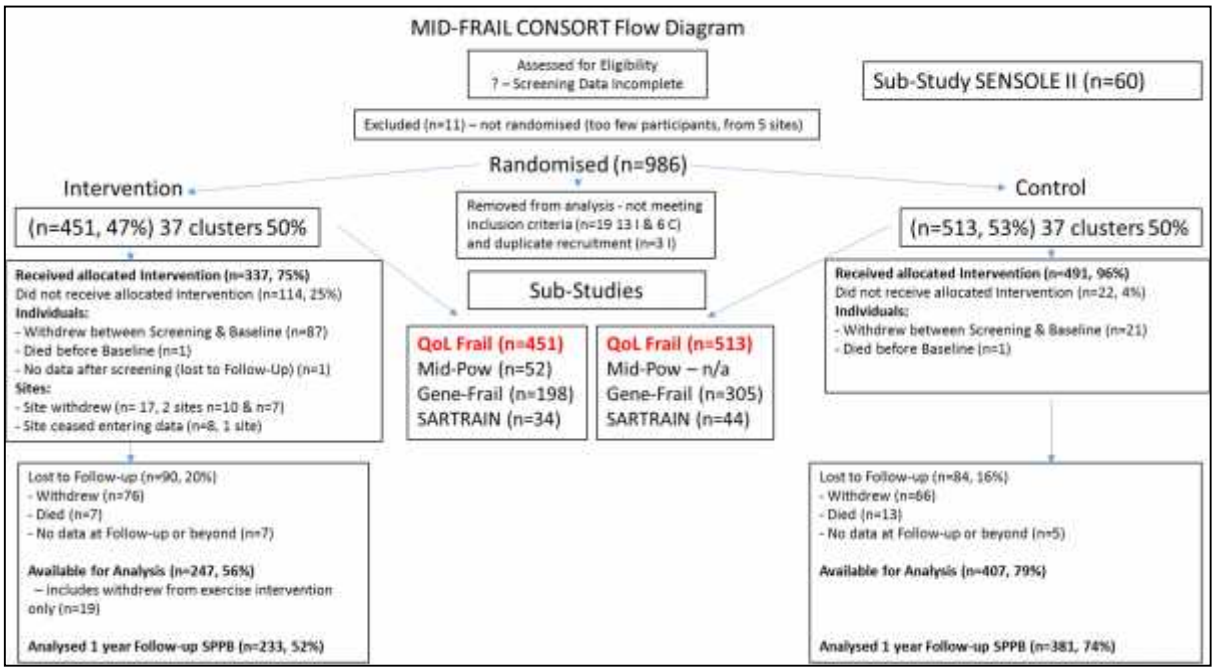
4. MID Frail Secondary analysis

Preliminary results don´t show clinically relevant or statistically significant treatment effects for either IADL, Barthel or EQ-5D-5L. Very few carers were recruited into the study and therefore this comparison is much unpowered and has wide confidence intervals.

5. Report of preliminary analysis of the QoL outcomes

The QoL Frail substudy is focused on the effects of the MID Frail intervention on quality of life (QoL) as part of the secondary outcomes of the main MID-FRAIL study. In addition, QoL Frail investigates the validity of the ADDQoL-Senior instrument which was specifically designed to appraise the impact of diabetes on QoL in older persons.

All subjects included in the MID-FRAIL study were invited to participate in the QoL assessment (see figure). There were no additional in- or exclusion criteria. (figure 9)



a) ADDQoL-Senior

The ADDQoL-Senior questionnaire consists first in 2 overview items scoring

1/ the 'present QoL' ("In general, my present QoL is…") scored on a 7-point Likert scale ranging from -3=extremely bad to +3=excellent,

2/ the 'diabetes-dependent QoL' ("If I did not have diabetes, my QoL would be …") scored on a 5-point Likert scale ranging from -1=worse to +3=very much better.

Next, the ADDQoL-Senior contains 17 domain-specific items of QoL for which the impact of diabetes is scored similarly as for the overall 'diabetes-dependent QoL'. In addition, the importance of these 17 domains are scored on a 4-point Likert scale ranging from 0=not important to +3=very important. The multiplication of impact*importance score provides a weighed score for each of the 17 items.

b) EQ5D

The EQ5D questionnaire consists in 2 parts:

1/ 5 questions concerning 5 domains scored on a 5-point Likert scale ranging from +1=no problems to +5=extreme problems; generating a total sumscore ranging from +5 to +25.

2/ a VAS for QoL ranging from 0=worst imaginable health state to 100=best imaginable health state.

The results of this preliminary analysis show that the MID-FRAIL intervention induced significant improvement of QoL in older patients with diabetes. Especially the ADDQoL-Senior was sensitive for detecting differences between changes in QoL after 1 year between intervention and control. EQ5D scores were significantly related to the item 'general health' of the ADDQoL-Senior, which can be explained by the rather generic QoL domains measured with EQ5D. Further analysis of the data for impact of diabetes on the ADDQoL-Senior subdomains will enable us to identify on which specific QoL domains relevant for older diabetes patients the MID-FRAIL intervention had substantial effects.

6. Results from the Health Economic Assessment

As it has been mentioning throughout this report, diabetes mellitus leads to multiple complications and its functional impairment is a major problem affecting individual autonomy and quality of life. Consequently, substantial health-care costs are associated with its management in terms of treatment, hospitalizations, emergency consultations, visits to General Practitioners (GPs) and other specialists, social services and family support. Overall, such disease might lead to a high utilization of resources (both health and non-health resources), considering diabetes as an illness with a significant economic impact. Additionally, as occurs with diabetes, frailty also leads to functional impairment, affecting individual autonomy and social well-being. Consequently, frailty has been associated with an increased use of health and community services (García-Nogueras et al.; Bock et al. 2016). Nevertheless, no evidence exits about the economic impact among frail people suffering from diabetes.

The MID-Frail project focuses on the use of interventions (exercise and nutritional programs) designed to improve functional status and enhance quality of life by acting on the mechanisms involved in producing frailty and its progression to adverse outcomes in people suffering from diabetes and frailty. The evidence about the effectiveness of such type of interventions is ambiguous.

However, due to that resources are scarce and budgets are limited, it is necessary to make decisions about how to invest these resources in the most efficient way. Therefore, economic evaluations are useful tools that provide quality information on the costs and

health outcomes of different alternatives in order to include the efficiency dimension in the decision-making process. Although some programs generate savings, a large number of them required an additional investment (higher cost). In fact, several analyses concluded that there was no improvement in health outcomes or it was very small (and cost effectiveness ratios are very high).

The main aim of the health economic assessment is to estimate the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR) of the multi-modal intervention in frail and pre-frail subjects aged ≥ 70 years with T2D in comparison with usual care.

More precisely, the main targets of the health economic assessment are:

a) To estimate the cost related to visits to general practitioner, specialist, nurse and emergency service, medical tests, hospitalization, and formal and informal caregiving during the one year-follow up period.
b) To test whether there are statistical differences in costs between intervention (IG) and usual care (UG).
c) To test whether the intervention is a cost-effective option in comparison with usual care during the one year-follow up period.

Results

The health economic assessment showed that both healthcare and non-healthcare costs of the patients who participated in the intervention program were equal to or lower than the costs of patients who participated in the control group (usual care). The cost of the investment in machinery, training and location required by the intervention program was offset by savings in lower hospitalization costs during the first year of follow-up. In terms of non-healthcare costs, lower costs were also observed in patients assigned to the intervention group versus the usual care group, although the differences were not statistically significant. In this sense, the high variability in costs found in both groups should be noted. It is also worth noting the large differences found in the cost of the intervention in each country (machinery costs, training costs and the cost of locating machines). A future challenge is to find the optimal use of resources to take advantage of potential economies of scale in the implementation of the intervention program. This would allow access to the program to a greater number of patients, with the added advantage that the average cost per patient would be reduced consistently.

The economic evaluation shows that, regardless of the chosen health indicator (SPPB score, percentage of patients with improvement in SPPB score ≥ one point or QALYs), the intervention dominates usual care. That is, the intervention program achieves better health outcomes at the same or lower cost than usual care. Therefore, the intervention program is efficient compared to usual care. The sensitivity analyses performed show that the results are consistent and the conclusions are robust, independently of the changes performed in the parameters and in the variables considered.

7. Safety

There have been 334 SAEs since the beginning of the study. Only one classified as related to the intervention. Since the beginning of the study eight SAEs are related to a subject enrolled in Sensole (one in Part 1 and seven in Part 2). All other SAEs related to subjects enrolled in the main MID-frail study.

The classification of SAES by disease area is showed in the next table: (figure 10)

Disease Area	Related n(%)	Not Related n(%)
Cardiac disorders	0	58 (100)
Respiratory	0	3 (100)
Musculoskeletal and connective tissue disorders	0	42 (100)
Nervous system disorders	0	38 (100)
Gastrointestinal disorders	1 (3)	32 (97)
Endocrine disorders	0	27 (100)
Renal disorders	0	21 (100)
Hepatic and hepatobiliary disorders	0	13 (100)
Urinary disorder	0	11 (100)
Dermatology disorders	0	9 (100)
Mental disorders	0	8 (100)
Blood and lymphatic system disorders	0	7 (100)
Unknown	0	7 (100)
Musculoskeletal pain	0	6 (100)
Reproductive disorders	0	4 (100)
Ocular disorder	0	3 (100)
Vascular disorder	0	3 (100)
Immune disorders	0	1 (100)

The rest of analysis will be submitted in a separate document when are available.

8. Ethics

The clinical trial has been conducted under the ethics principles, the applicable legislation, in accordance with the protocol and following a complete program of Standard Operating Procedure.

All amendments have been submitted to the ERB and other Regulatory Authorities following the legislation requirements in each country.

Updated reports have been submitted annually to the Ethics Committees involved in MID Frail project.

4. The potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results.

Potential impact

The idea of the MIDFRAIL STUDY was shaped in 2010, in the context of a research group that was completing a Coordination and Suport action ("*Frailty Operative Definition-Consensus Conference" -FOD CC, 261270-*) focused on the specific topic of Frailty. The group consisted of researchers with a remarkable background in Frailty, but several of them, also with an outstanding knowledge in diabetes in older people.

Therefore, the publication in 2010 of the call *FP7-HEALTH-2011-two-stage* was a very exciting challenge for this group. Indeed, the topic *HEALTH.2011.2.2.2-1 (Investigator-driven clinical trials for therapeutic interventions in elderly populations)* marked a series of priorities and the aim of achieve several impacts that coincided with some research ideas on both Prof. Rodriguez Mañas and Prof. Sinclair had been thinking about for a long time. This way the enthusiastic team started working on a proposal several months before the publication of the call, based on the analysis of successive drafts.

The topic aimed at supporting a project capable to respond to several challenges. Besides the impacts of a clinical nature (such as *healthy ageing improvement at a European level*), the project also had to result in a clear societal and economic impact such as (a) a significant impact on Healthcare cost reduction, (b) contribution to jobs creation, (c) encouraging the active participation of SMEs thus boosting their development at European level, (d) participation of patient advocacy groups and networks, and (e) creation of opportunities for young researchers.

Therefore, the project needed to go beyond to responding to the clinical challenges posed by the call, but also needed a broad and multidisciplinary vision and ambition to tackle those other impacts. The consortium, therefore, could not be limited to some of the most brilliant clinical research groups on frailty and / or diabetes in older people. By contrast, the project needed to involve, in the consortium, groups and entities with very different expertise, and the participation of these groups and organizations needed to be very active from the inception and based on an equal footing with clinical partners. Although the topic indicated that the collaborative project had to adopt the form of a *Small or medium-scale focused research project*, the fact is that the complexity of the objectives proposed led us to form a consortium involving 16 full partners.

All these partners, with such different capacities, visions and expertise, had to participate in the of the project design from the very beginning. Only this way the project could respond to so many and varied challenges.

For this reason, it was decided to include companies, preferably SMEs. But not anyone. Three companies were gradually invited (Igen Biotech SL, Hexabio SARL and Niche Science & Technology Ltd). Later, with the project already ongoing, the consortium included Diabetes Frail as well, a Non For Profit small entity focused on diabetes in Older People, led by Prof. Sinclair, scientific coordinator of the study. The choice of these SMEs was not accidental.

- Igen, a promising biotechnological Spanish SME was an ideal partner to be involved in one of the substudies (*GENEFRAIL*), participating in the development

of genetic and epigenetic instruments to examine risk factors for disability development and predicting response to treatment.

- Hexabio, a very suitable candidate to participate in the specific substudy *SENSOLE*.
- Niche Science & Technology, provided high expertise and experience in the design and running of the health communication and dissemination activities. In addition, Niche could develop tasks of CRO. This was especially helpful for the setting up and implementation of the contingency measures adopted after termination of CAIBER.

The MIDFRAIL consortium also incorporated one of the best groups in Spain on research on health analysis (UCLM led by Prof. Juan Oliva), since the precise calculation of healthcare costs savings due to the project, had to be properly analysed in order to provide conclusive evidence of the economic impact of the study.

The results of the intervention needed to be properly assessed, and that made necessary a strong data analysis. Thus, a solvent group to carry out the statistical analysis was also included (The group of Prof. Bayer / Prof. Hood at Cardiff University).

The clinical groups completed the consortium. For all of them, it was mandatory not only a PI with an excellent research background in the field, but also a group accrediting the necessary experience, publications, etc and institutions with sufficient capability and infrastructures to ensure a proper management of project workplan, resources and commitments. The topic required involve Patient advocacy groups and support networks, and that was met by including a good number of diabetes patient´s advocacy groups and of existing supporting networks, thus taking advantage of several results already reached in this topic and exploiting synergies with them.

The call also required to ensure that a sufficient number of patients from different age ranges and health status could be recruited. For this purpose, MIDFRAIL set up a consortium and a workplan which has involved more than 100 collaborating recruiting centres (trial sites), thus ensuring a high recruitment capacity.

The consortium had indeed the capabilities to develop a project that would respond to the expected impacts set in the call. It was necessary to design a workplan that would meet all the challenges required from all points of view foreseen in the call. In addition, each one of these impacts needed to be correctly measured, during the course of the project, and at its end.

Specifically, according to the topic and the call, the project was required to achieve the following expected impact:

> *The funded projects should contribute to better clinical management of the elderly with the potential to reduce healthcare costs while ultimately improving healthy ageing of European senior citizens. A strong participation of SMEs in the projects should help ensuring innovation in this area/topic. The degree of active participation of research-intensive SMEs will be considered during the evaluation*

Therefore, MIDFRAIL had to respond to the following challenges:

- Contribute to better clinical management of the elderly,
- Potential to reduce healthcare costs

- Improving healthy ageing of European senior citizens
- Strong participation of SMEs (mainly research-intensive SMEs) in the project thus help ensuring innovation in this topic.

The achievement of any of these impacts would have already been a remarkable advance. However, MIDFRAIL has achieved all the impacts described in the topic. In addition, the project has had other impacts that must be placed value on. Below, the main impacts of MIDFRAIL are listed, both from a clinical / scientific view and from the perspective of other kind of impacts such as social and economic ones:

a) Clinical impact: Improvement in the healthy aging and living conditions of older patients and improvement of the clinical management of the older patients with diabetes.

MIDFRAIL STUDY shows the effectiveness of a 16-week multimodal intervention consisting of education, strength training and pharmacological treatment optimization to achieve glycosylated hemoglobin and blood pressure targets in accordance with published guidelines for this frail older population.

The intervention has shown to improve the function of the frail and pre-frail older population with diabetes, measured through the Short Physical Performance Battery (SPPB) in a clinically relevant way, with statistically significant improvements.

Despite the high number of withdrawals in the early stages of the study, the rate of adherence to the intervention was high (80%), suggesting that short-term interventions would be more appropriate, since this type of study requires the commitment of the subject, the research team, and the relatives or caregivers.

Although a large number of serious adverse events have been reported throughout the follow-up of the study, only 1 of them has been linked with the intervention, so it can be considered safe.

This clinical trial opens the way to new research initiatives, some of them already ongoing, and to interventions based on physical exercise with the aim of preventing or delaying the development of disability in the elderly.

Improvement in the quality of life of patients

The results of this preliminary analysis show that the MID-FRAIL intervention induced significant improvement of QoL in older patients with diabetes. Especially the ADDQoL-Senior was sensitive for detecting differences between changes in QoL after 1 year between intervention and control. EQ5D scores were significantly related to the item ‘general health’ of the ADDQoL-Senior, which can be explained by the rather generic QoL domains measured with EQ5D. Further analysis of the data for impact of diabetes on the ADDQoL-Senior subdomains will enable us to identify on which specific QoL domains relevant for older diabetes patients the MID-FRAIL intervention had substantial effects

b) Significant cost savings: Potential to reduce healthcare costs

The health economic assessment showed that both healthcare and non-healthcare costs of the patients who participated in the intervention program were equal to or lower than the costs of patients who participated in the control group (usual care). The cost of the

investment in machinery, training and location required by the intervention program was offset by savings in lower hospitalization costs. In terms of non-healthcare costs, lower costs were also observed in patients assigned to the intervention group versus the usual care group, although the differences were not statistically significant. In this sense, the high variability in costs found in both groups should be noted. It is also worth noting the large differences found in the cost of the intervention in each country (machinery costs, training costs and the cost of locating machines). A future challenge is to find the optimal use of resources to take advantage of potential economies of scale in the implementation of the intervention program. This would allow access to the program to a greater number of patients, with the added advantage that the average cost per patient would be reduced consistently.

The economic evaluation shows that, regardless of the chosen health indicator, the intervention dominates usual care. That is, the intervention program achieves better health outcomes at the same or lower cost than usual care. Therefore, the intervention program is efficient compared to usual care. The sensitivity analyses performed show that the results are consistent and the conclusions are robust, independently of the changes performed in the parameters and in the variables considered.

Specific figures cannot be disclosed in this publishable summary, since detailed results and conclusions will be object of publications.

c) Active participation of research-intensive SMEs and related benefits for them, the European SMEs and innovation in the topic

MIDFRAIL has involved from the beginning three SMEs, which have played a fundamental role in the project since its inception. Two of them, IGEN and HEXABIO, have developed a leadership role in the design and implementation of two of the sub-studies of the work package 6.

Both companies have taken advantage of the collaboration of MIDFRAIL to extend its network, of clients, expand its alliances with other research entities and intensify its participation in new projects, as well as to improve its possibilities of development and commercialization of its products.

In the case of Niche, his role was key, and even more after CAIBER's termination, since CAIBER was to have an essential role in the project as a kind of CRO linked to the ECRIN network, was to would provide the monitoring and follow-up work of the Trial throughout Europe.

After CAIBER’s termination, these tasks were distributed between the coordinator and NICHE, who took on several of them. This SME has also extended its network of alliances and collaborations in research projects and initiatives. For example, NICHE participates as full beneficiary as the dissemination leader in the FRAILOMIC project (FP7 305483), also focused on frailty.

With the project already ongoing, another small, non-profit entity, Diabetes Frail Ltd., joined the consortium taking on the key tasks (including the scientific coordination) initially assigned to the Institute of Diabetes for Older People, University of Bedfordshire.

Thus, the participation of SMEs has been key in the project. In adition, all of them have benefited from their incorporation into this study. Therefore, MIDFRAIL has significantly contributed, within its possibilities, to the development of the economic

activity of some European SMEs. If we also consider the indirect benefits of SMEs that have been hired / subcontracted by the project participants, the impact is even greater on the activity and performance of a large number of European SMEs. In this sense, we must also say that the project has also benefited from the enthusiasm and high professionalism with which these companies have carried out their tasks.

d) Participation of patient advocacy groups and networks.

According to the topic's needs, the consortium, as such, involved, from the beginning the participation of some of the most relevants newtworks and patient advocacy groups, such as Diabetes UK, the Coordination and Support Action FOD-CC (FP7-HEALTH-2010-single-stage-261270-FOD-CC) also coordinated by MIDFRAIL's coordinator and also focused on Frailty, as well as GERONTONET, ECRIN Network.

In addition, according to the initial plan, the partners made contacts with networks and groups in their respective countries, such as Belgian Society for Gerontology and Geriatrics; Belgian Diabetes Association; Czech Society of Diabetology; Czech Society of Gerontoly and Geriatrics; Czech medical Association; Czech Union of Retired Persons (Svaz duchodcu CR); InVS (Health watch); INPES (national institute for health education); French Gerontological and geriatric society; Deutsche Diabetes-Stiftung DDS (German Diabetes Foundation); Deutsche Diabetes-Gesellschaft" DDG (German DIabetes Association); Deutsche Gesellschaft für Geriatrie DGG (German Geriatric Association); Italian Society of Diabetologia -S.I.D.; Italian Society of Gerontology ; Geriatrics - S.I.G.G.; Sociedad Española de Medicina Geriátrica, SMEG; Academia Latinoamericana de Medicina del adulto mayor - ALMA; Diabetes UK; Older people and Ageing Research Network (OPAN); National Institute for Social care and health research (NISCHR) and the British Geriatrics Society.

The contribution of these entities, networks and groups has been very valuable, since they have allowed the project to be designed from the beginning taking into account the opinion and inputs from many of the most relevant stakeholders in the field, who have been able to contribute to the co-creation of the study.

e) Key female participation

In MIDFRAIL, the participation of females has been key. The majority of researchers involved in the project are female; they have carried, on their shoulders, most of the project burden. In addition, two of the principal Investigators are females (Profs. Bourdel-Marchasson –WP6 leader- and Topinkova), as well as most of the project managers.

f) Opportunities for young researchers.

Midfrail has been a great opportunity for dozens of young researchers. Because of the project, the participating partners have hired or maintained in their staff a large number of researchers, many of them in early stage of their careers. It is also worth noting that, in some cases, the work carried out in MIDFRAIL and part of its findings will form part of the doctoral thesis presented by Olga Laosa. This project has been certainly a significant milestone in the research career of several young researchers, and their results will be the subject of discussion and new scientific initiatives in the near future.

g) Other impacts: The need for a harmonization of the legislation and rules applicable to clinical trials in Europe.

Another impact of MIDFRAIL, not considered initially, is that during the course of the project it has been revealed the enormous bureaucratic and legal difficulties faced by the international multicentric clinical trials on this type of population conducted by independent researchers.

The course of MIDFRAIL has revealed the serious difficulties derived from the very different legislations, requirements and deadlines in each country. This has been an issue that the study has had to deal with and overcome. This obstacle has meant a significant delay in the study and a notable increase in related costs (both in terms funds and in terms of staff involvement in person months) needed to successfully conclude the trial and correctly overcome all the administrations steps, which are extremely heterogeneous along the different countries.

Thus, MIDFRAIL has brought to light the urgent need for a harmonization of the rules applicable to clinical trials in Europe.

Explotation of results

The Communications Strategy for the MID-Frail study has presented and emphasised the key characteristics of the project. The study is original, with both the intervention and outcomes being unique for studies in diabetes, relevant, addressing a topic with multiple stakeholders, including patients, carers, health care practitioners and health care providers, pertinent, being focused on function, which is the main component of quality of life and the most important outcome in this population, and feasible, as it has been carried out by senior researchers with previous relevant contributions in the fields of frailty and diabetes and their complications in older people.

Dissemination of the MID-Frail Key Messages has involved a range of activities designed to achieve the greatest possible awareness of the study, its aims and methodology, results and conclusions. Informing stakeholders of the implications of the study has willing to led to a change in the clinical management of older people with diabetes, with resulting clinical, economic and social benefits across the European Union.

A series of **strategic publications** have been performed to raise awareness of the study and to continue to develop the MID-Frail brand. This ensured that study data are anticipated and receive maximum attention upon release.

Midfrail database was locked in the last 30 April 2017. Therefore, the main results have been analysed after this date. These results will be published in the coming months. The rest of results (secondary outcomes, substudies , etc…) will be published coming soon as well. Up to now, only the protocol has been published: An evaluation of the effectiveness of a multi-modal intervention in frail and pre-frail older people with type 2 diabetes--the MID-Frail study: study protocol for a randomised controlled trial, Trials 2014; 15:34.

This is a **journal of high impact** from the relevant fields of gerontology and diabetes as "**Trials Journal**", an open access peer-reviewed medical journal covering performance and outcomes of randomized controlled trials. Research Gate (www.researchgate.net) shows the article to have been downloaded 621 times during the life of the project and an Impact Factor of 2.16. Diabetes and Frailty: Two Converging Conditions (with citation to MID FRAIL) was published in Canadian Journal of diabetes with an Impact Factor of 1.86. Both of them are indexed at ´**NCB Pubmed**´ that comprises more than 27 million citations for biomedical literature from MEDLINE, life science journals, and online

books. National scope journals have been also targeted to disseminate MID-FRAIL project.

The MID-Frail Intellectual Property Committee (IPC) has as one of its key tasks to oversee and approve all MID-Frail-related publications (including abstracts, posters and oral presentations at conferences) and patent applications. Previously, this process has been organised and tracked by Niche Science and Technology (NST) but both MIDFRAIL coordinators now wish to revise the scheme for submitting potential publications by making all requests for submission of a paper/manuscript to be dealt with by the Coordinators' Offices in London and Madrid.

A priority list of publications has been designed to disseminate the results of the MID Frail project in the scientific community.

Proposed Priority List:

1- **Main EU-wide RCT** - a manuscript based on SPPB and functional change, and all primary outcomes at 1-year: **SPPB + ADL change + IADL Change** (ADL + IADL are listed as secondary outcomes)
2- **Factors influencing/affecting primary outcomes** (+ 18/24 month outcomes)
3- **A manuscript based on the analysis of secondary outcomes**:

Other Secondary Outcomes are:

- Episodes of symptomatic hypoglycaemia (i.e. a recorded blood sugar less than 4mmol/l, or symptoms or signs attributed to low blood sugar and responding to appropriate treatment))
- Episodes of hospital admission (i.e. any admission involving an overnight stay)
- Episodes of permanent institutionalization (i.e. a permanent move to any care setting other than the patient's own home, where paid staff are available to provide care if needed at any time during the day or night).
- Burden of the Carer, as assessed by the Modified Caregiver Strain Index (Sinclair AJ et al., 2010)
- Overall mortality

4- Analysis of economic measures:

5- Mid-POW

6- Sensole:

7- Gene Frail:

8- Metabofrail

9- Sartrain:

10- A manuscript based on quality of life/validation of ADDQol Senior:

All these articles will be published in the coming months.

Data from the main study has been be presented at **relevant congresses.**

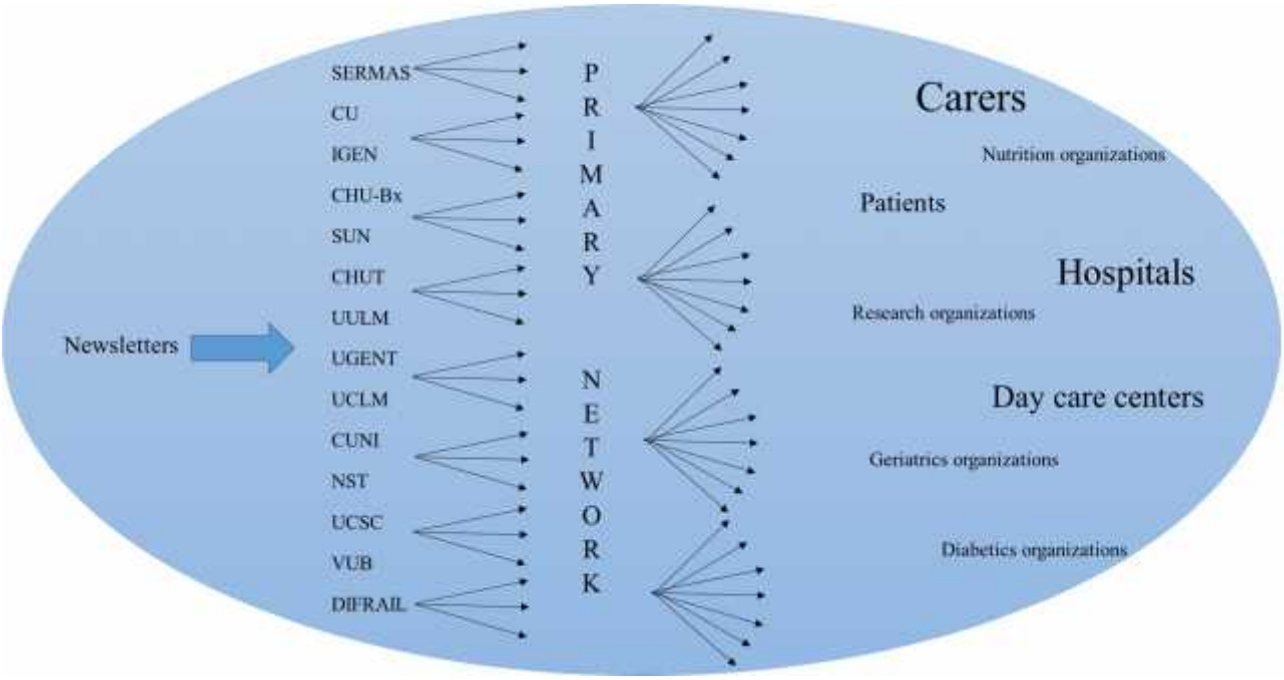
The table below summarizes the events that Mid-Frail consortium attended. Submitted presentations have taken the form of keynote speaker presentations, oral communications and posters, in order of preference.

Event	Date	Partners	Type of presentation	Type of Audience - Scope
7th International Academy on Nutrition and Aging Conference (IANA 2012)-Albuquerque, New Mexico, USA	12th-13th July 2012	CHU-Bx	Project presentation. Oral communication	Scientific->100
V Memorial Dr.Guillen Llera: integrated management of elderly patients with diabetes: A clinical challenge, which took place at the University Hospital of Getafe, Madrid, Spain	8th March 2012	SERMAS	Project presentation. Oral communication	Scientific->50
Journal of Frailty and Aging. 2012	2012	CHU-Bx, SERMAS, DIFRAIL	Abstract	Scientific->1,000
Academia Latinoamericana del Adulto Mayor (ALMA) course in Buenos Aires, Argentina.	September 2013	SERMAS	Project presentation. Oral communication	Scientific->1,000
10th Congrès International Francophone de Gérontologie et Gériatrie. Liège, Belgium	14th – 16th May 2014	CHU-Bx, SERMAS, DIFRAIL	Project presentation. Oral communication	Scientific->1,000
Congrès Annuel de la Société Francophone du Diabète. Paris, France.	11th – 14th March 2014	CHU-Bx, SERMAS, DIFRAIL	Poster communication.	Scientific->4,000
International Academy on Nutrition and Aging Conference. Barcelona, Spain	18th - 19th June 2015	CHU-Bx, CU	Abstract and Poster communication	Scientific
59th Congress of Italian Society of Geriatrics. Italy	n/a	All	Project presentation. Oral communication	Scientific
Public Health Showcase event. Wales	November 2015	CU	Project presentation. Oral communication and Poster communication	Scientific and Policy makers->100
Annual meeting of the Czech Society of Gerontology and Geriatrics. Czech republic.	2014	CUNI	Project presentation. Oral communication	Scientific->1,000

Event	Date	Partners	Type of presentation	Type of Audience - Scope
Czech Society of General Practice	2015	CUNI	Project presentation. Oral communication	Scientific->100
Annual congress of the Czech Society of Internal Medicine in Prague, Czech Republic.	2015	CUNI	Project presentation. Oral communication	Scientific->1,000
Regional conference "Gerontology days". Ostrava, Czech Republic.	2015	CUNI	Project presentation. Oral communication	Scientific->800
Annual Congress of the Czech Society of Gerontology and Geriatrics in Hradec Kralove, Czech Republic	November 2016	CUNI	Project presentation. Oral communication	Scientific->300
Annual Congress of the Czech Society of Internal Medicine. Czech republic	September 2016	CUNI	Project presentation. Oral communication	Scientific->800

Data from the substudies have been mainly presented at **specialist meetings and investigators from trial sites** with the commitment of spreading the results among different stakeholders (carers and patients).

The designated purpose of the newsletter was to distribute information among the partner organisations to update them on the progress of the study in an electronic format that was further distributed across their institutions and broader networks, informing the diabetes community about MID-Frail. **7 newsletter** were distributed along the project duration. In the workflow below is showed how the dissemination of the newsletters has been performed. A high impact on dissemination has been estimated due to the huge network of the partner from the consortium.



Newsletters dissemination scope

Press releases have been delivered along the project duration. The MID-Frail press release has been submitted to more than 15 online news services.

The MID-Frail study web address (www.midfrail-study.org) was registered immediately that the study was approved (Nov 2011).

5. Project public website

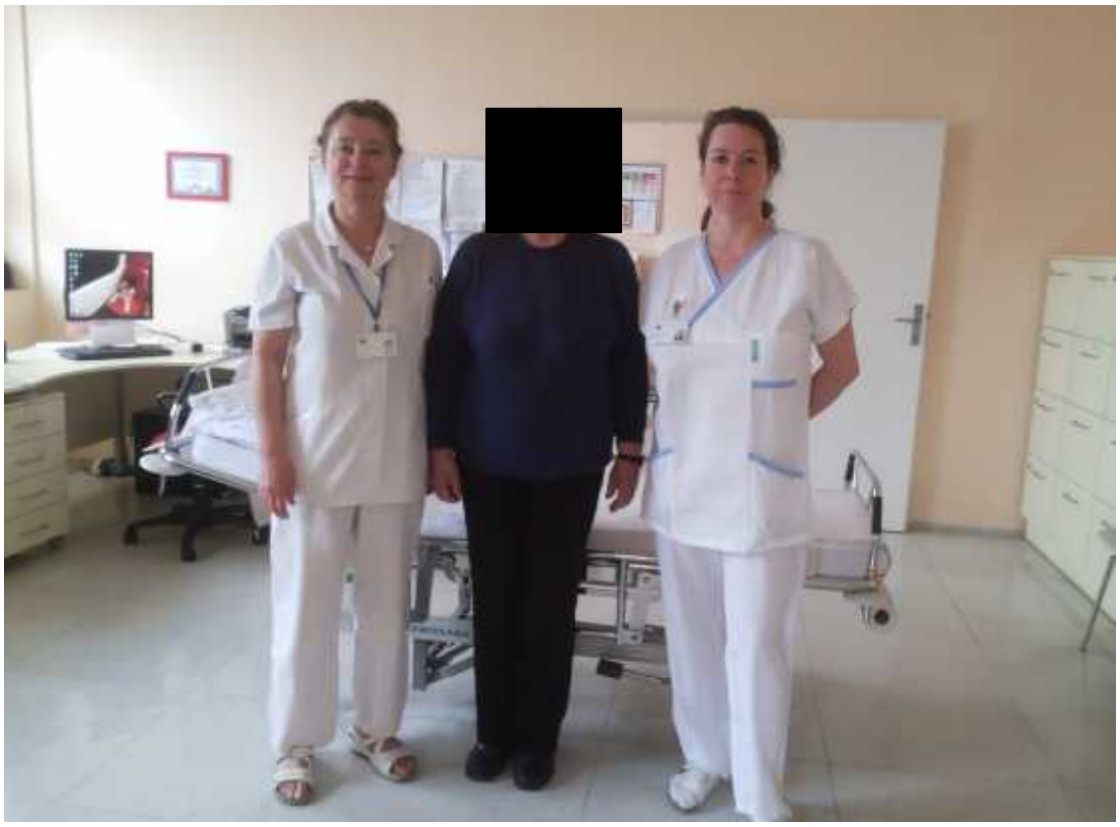
http://midfrail-study.org/

This page will be updated when results are published.

Mid Frail Logo:

Mid Frail website landing page:

Photos:



First participant finished in Czech Rep.

First participant finished in Spain

Educational session

Resistance training

Final meeting (Alcala de Henares April 2017)

Final meeting (Alcala de Henares April 2017)

6. Use and dissemination of foreground

Section A (public)

A1: LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS, STARTING WITH THE MOST IMPORTANT ONES

NO.	Title	Main author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Permanent identifiers[2] (if available)	Is/Will open access[3] provided to this publication?
1	An evaluation of the effectiveness of a multi-modal intervention in frail and pre-frail older people with type 2 diabetes--the MID-Frail study: study protocol for a randomised controlled trial	Rodríguez-Mañas	Trials	Nº 15; Jan 2014		e BioMed Central Ltd	2014	pp. 34-42		yes

[2] A permanent identifier should be a persistent link to the published version full text if open access or abstract if article is pay per view) or to the final manuscript accepted for publication (link to article in repository).

[3] Open Access is defined as free of charge access for anyone via Internet. Please answer "yes" if the open access to the publication is already established and also if the embargo period for open access is not yet over but you intend to establish open access afterwards.

NO.	Type of activities	Main leader	Title	Date/Period	Place	Type of audience	Size of audience	Countries addressed
1	Conference	CHU-Bx	7th International Academy on Nutrition and Aging Conference (IANA 2012)	12th-13th July 2012	Albuquerque, New Mexico, USA	Scientific	>100	International
2	Conference	SERMAS	V Memorial Dr.Guillen Llera: integrated management of elderly patients with diabetes: A clinical challenge, which took place at the University Hospital of Getafe.	8th March 2012	Madrid, Spain	Scientific	>50	Spain
3	Publication	CHU-Bx, SERMAS, DIFRAIL	Journal of Frailty and Aging. 2012	2012	-	Scientific	>1,000	Global
4	Conference/Poster	SERMAS	SEMEG congress Toledo 2012	2012	Toledo, Spain	Scientific	>1000	Spain
5	Conference	SERMAS	Academia Latinoamericana del Adulto Mayor (ALMA) course in	September 2013	Buenos Aires, Argentina.	Scientific	>1,000	LATAM
6	Conference	CHU-Bx, SERMAS, DIFRAIL	10th Congrès International Francophone de Gérontologie et Gériatrie.	14th – 16th May 2014	Liège, Belgium	Scientific	>1,000	International

NO.	Type of activities	Main leader	Title	Date/Period	Place	Type of audience	Size of audience	Countries addressed
7	Conference/Poster	CH11U-Bx, SERMAS, DIFRAIL	Congrès Annuel de la Société Francophone du Diabète.	11th – 14th March 2014	Paris, France	Scientific	>4,000	France
8	Conference	SERMAS	MID-FRAIL, a different approach to the older adults with diabetes	23th April 2015	Boston, EEUU	Scientific	>5000	
9	Poster/Publication	CHU-Bx, CU	International Academy on Nutrition and Aging Conference.	18th - 19th June 2015	Barcelona, Spain	Scientific	n/a	International
10	Conference	All	59th Congress of Italian Society of Geriatrics.	n/a	Italy	Scientific	n/a	Italy
11	Poster	CU	Public Health Showcase event.	November 2015	Wales	Scientific and Policy makers	>100	Wales
12	Conference	CUNI	Annual meeting of the Czech Society of Gerontology and Geriatrics.	2014	Czech Republic	Scientific	>1,000	Czchec Republic
13	Conference	CUNI	Czech Society of General Practice	2015	Czech Republic	Scientific	->100	Czchec Republic
14	Conference	CUNI	Annual congress of the Czech Society of Internal Medicine in Prague, Czech Republic.	2015	Czech Republic	Scientific	>1,000	Czchec Republic

NO.	Type of activities	Main leader	Title	Date/Period	Place	Type of audience	Size of audience	Countries addressed
15	Conference	CUNI	Regional conference "Gerontology days". Ostrava, Czech Republic.	2015	Czech Republic	Scientific	>800	Czchec Republic
16	Conference	CUNI	Annual Congress of the Czech Society of Gerontology and Geriatrics in Hradec Kralove, Czech Republic	November 2016	Czech Republic	Scientific	>300	Czchec Republic
17	Conference	CUNI	Annual Congress of the Czech Society of Internal Medicine. Czech republic	September 2016	Czech Republic	Scientific	>800	Czchec Republic
18	Conference /Poster	SERMAS	SEMERGEN congress 2015	14-17 October 2015	Valencia, Spain	Scientific	>5000	Spain
19	25 Newsletters	NTS	Newsletter			Scientific, Policy makers, Carers, Patients		International
20	Press-release	NTS	Sweet Frailty: http://www.fyi-news.co.uk/sweet-frailty	June 2013		Scientific, Policy makers, Carers, Patients	38,000	International
21	Press release	SERMAS	El H2020 como guía para la evaluación de la tecnología sanitaria	22-28 June 2015	Madrid	All	>1000	

NO.	Type of activities	Main leader	Title	Date/Period	Place	Type of audience	Size of audience	Countries addressed
22	Article published in the popular press	SERMAS	Ejercicio y más control para mejorar la diabetes	April 2017		All	>50,000	Spain
23	Press releases	SERMAS	El Hospital de Getafe impulsa mejoras en la calidad de vida de las personas mayores con diabetes	April 2017		All	>1,000	Spain
24	Press releases	SERMAS	El Hospital de Getafe impulsa mejoras en la calidad de vida de las personas mayores con diabetes	April 2017		All	>1,000	Spain
25	Press releases	SERMAS	Ejercicio y mayor control de la diabetes mejorarían la funcionalidad de los mayores	April 2017		All	>1,000	Spain
26	Press releases	SERMAS	Madrid. el consejero de Sanidad acude al cierre del proyecto Midfrail del Hospital de Getafe	April 2017		All	>1,000	Spain
27	Press releases	SERMAS	Madrid. el consejero de sanidad acude al cierre del proyecto midfrail del hospital de getafe	April 2017		All	>1,000	Spain
28	Article published in the popular press	SERMAS	El hospital de Getafe impulsa mejoras en la vida de los mayores con diabetes	April 2017		All	>1,000	Spain
29	Press releases	SERMAS	El Hospital de Getafe impulsa mejoras en la calidad de vida de las personas mayores con diabetes	April 2017		All	>1,000	Spain

NO.	Type of activities	Main leader	Title	Date/Period	Place	Type of audience	Size of audience	Countries addressed
30	Press releases	SERMAS	El hospital de Getafe impulsa mejoras en la vida de los mayores con diabetes	April 2017		All	>1,000	Spain
31	Press releases	SERMAS	El hospital de Getafe impulsa mejoras en la vida de los mayores con diabetes	April 2017		All	>1,000	Spain
32	Press releases	SERMAS	EL CONSEJERO DE SANIDAD ACUDE AL CIERRE DEL PROYECTO MIDFRAIL DEL HOSPITAL DE GETAFE	April 2017		All	>1,000	Spain
33	TV	SERMAS	Informativo de Madrid 2 – 24/04/2017	April 2017		All	>100,000	Spain
34	Website	NTS	http://midfrailstudy.com/	2012		All	n/a	Global
35	Publication	UULM	Europäisches Konsortium Diabetes und Alter – Individuelle Behandlung ist notwendig	2013		Scientific	n/a	Germany
36	Presentation	UULM	Midfrail in 3 steps	April 2012		Scientific	n/a	International
37	Publication	UULM	Dagegen gibt es eine Therapie!	June 2012		Scientific	>170	Germany
38	Publication	UULM	Im Alter individuell therapieren	2013		Scientific	n/a	Germany
39	Publication	SERMAS	MID-Frail protocol manuscript	January 2014		Scientific	>261	International

NO.	Type of activities	Main leader	Title	Date/Period	Place	Type of audience	Size of audience	Countries addressed
40	Publication	CUNI	The characteristics of diabetic residents in European nursing homes: results from the SHELTER study.	December 2014		Scientific		International

Section B (Confidential4 or public: confidential information to be marked clearly)

No applicable

7. Report on societal implications

A General Information *(completed automatically when **Grant Agreement number** is entered.*	
Grant Agreement Number:	**278803**
Title of Project:	A randomised clinical trial to evaluate the effectiveness of a multi-modal intervention in frail and pre-frail older people with type 2 diabetes: The MID-Frail study
Name and Title of Coordinator:	Dr. Leocadio Rodriguez Mañas, SERMAS, Servicio Madrileño de Salud (Hospital Universitario de Getafe

B Ethics	
1. Did your project undergo an Ethics Review (and/or Screening)? ⁾ If Yes: have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final project reports? Special Reminder: the progress of compliance with the Ethics Review/Screening Requirements should be described in the Period/Final Project Reports under the Section 3.2.2 *'Work Progress and Achievements'*	***YES***
2. Please indicate whether your project involved any of the following issues (tick box) :	***YES***
RESEARCH ON HUMANS	
⁾ Did the project involve children?	
⁾ Did the project involve patients?	X
⁾ Did the project involve persons not able to give consent?	
⁾ Did the project involve adult healthy volunteers?	
⁾ Did the project involve Human genetic material?	X
⁾ Did the project involve Human biological samples?	X
⁾ Did the project involve Human data collection?	X
RESEARCH ON HUMAN EMBRYO/FOETUS	
⁾ Did the project involve Human Embryos?	
⁾ Did the project involve Human Foetal Tissue / Cells?	
⁾ Did the project involve Human Embryonic Stem Cells (hESCs)?	
⁾ Did the project on human Embryonic Stem Cells involve cells in culture?	
⁾ Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?	
PRIVACY	
⁾ Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	X
⁾ Did the project involve tracking the location or observation of people?	X
RESEARCH ON ANIMALS	

[4] Note to be confused with the "EU CONFIDENTIAL" classification for some security research projects.

) Did the project involve research on animals?	
) Were those animals transgenic small laboratory animals?	
) Were those animals transgenic farm animals?	
) Were those animals cloned farm animals?	
) Were those animals non-human primates?	
RESEARCH INVOLVING DEVELOPING COUNTRIES	
) Did the project involve the use of local resources (genetic, animal, plant etc)?	
) Was the project of benefit to local community (capacity building, access to healthcare, education etc)?	
DUAL USE	
) Research having direct military use	
) Research having the potential for terrorist abuse	

C Workforce Statistics

3. Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator		2
Work package leaders	1	7
Experienced researchers (i.e. PhD holders)	7	15
PhD Students	8	10
Other	7	6

4. How many additional researchers (in companies and universities) were recruited specifically for this project?	**15**
Of which, indicate the number of men:	8

D Gender Aspects

5. Did you carry out specific Gender Equality Actions under the project?	X	Yes No

6. Which of the following actions did you carry out and how effective were they?

		Not at all effective				Very effective
X	Design and implement an equal opportunity policy	○	○	○	X	○
X	Set targets to achieve a gender balance in the workforce	○	○	○	○	X
❑	Organise conferences and workshops on gender	○	○	○	○	○
❑	Actions to improve work-life balance	○	○	○	○	○
○	Other:					

7. Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed?

x Yes- please specify : **Clinical trial has been focused in the similar way to men and women. In fact in recruitment, approximately 50% were men and 50% women. The results can be applied in the similar way to men and women and the social application could be similar to men and women as well**

No

E Synergies with Science Education

8. Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?

○ Yes- please specify

X No

9. Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?

X Yes- please specify: **DVD AND POSTER. Poster about diabetological education and DVD to researchers were designed to carry out the intervention during the study**.

○ No

F Interdisciplinarity

10. Which disciplines (see list below) are involved in your project?

3 Main discipline[5]: **medical sciences**

[5] Insert number from list below (Frascati Manual).

Associated discipline[5]: **3.1 (Basic medicine (anatomy, cytology, physiology, genetics, pharmacy, pharmacology, toxicology, immunology and immunohaematology, clinical chemistry, clinical microbiology, pathology)**	○	Associated discipline[5]: **3.2 (Clinical medicine (anaesthesiology, paediatrics, obstetrics and gynaecology, internal medicine, surgery, dentistry, neurology, psychiatry, radiology, therapeutics, otorhinolaryngology, ophthalmology)** Associated discipline[5]: **3.3 (Health sciences (public health services, social medicine, hygiene, nursing, epidemiology)**

G Engaging with Civil society and policy makers

11a Did your project engage with societal actors beyond the research community? *(if 'No', go to Question 14)*	○ Yes X No	

11b If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?

- ○ No
- ○ Yes- in determining what research should be performed
- ○ Yes - in implementing the research
- ○ Yes, in communicating /disseminating / using the results of the project

11c In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?	○ Yes ○ No	

12. Did you engage with government / public bodies or policy makers (including international organisations)

- ○ No
- ○ Yes- in framing the research agenda
- ○ Yes - in implementing the research agenda
- ○ Yes, in communicating /disseminating / using the results of the project

13a Will the project generate outputs (expertise or scientific advice) which could be used by policy makers?

- ○ Yes – as a **primary** objective (please indicate areas below- multiple answers possible)
- ○ Yes – as a **secondary** objective (please indicate areas below - multiple answer possible)
- ○ No

13b If Yes, in which fields?

Agriculture Audiovisual and Media Budget Competition Consumers Culture Customs Development Economic and Monetary Affairs Education, Training, Youth Employment and Social Affairs		Energy Enlargement Enterprise Environment External Relations External Trade Fisheries and Maritime Affairs Food Safety Foreign and Security Policy Fraud Humanitarian aid		Human rights Information Society Institutional affairs Internal Market Justice, freedom and security Public Health Regional Policy Research and Innovation Space Taxation Transport	

13c If Yes, at which level?

- ○ Local / regional levels
- ○ National level
- ○ European level
- ○ International level

H Use and dissemination

14. How many Articles were published/accepted for publication in peer-reviewed journals?	**1 (in the coming months several publications will be submitted including results)**
To how many of these is open access[6] provided?	**1**
How many of these are published in open access journals?	**1**
How many of these are published in open repositories?	**1**
To how many of these is open access not provided?	**0**
Please check all applicable reasons for not providing open access:	
❑ publisher's licensing agreement would not permit publishing in a repository ❑ no suitable repository available ❑ no suitable open access journal available ❑ no funds available to publish in an open access journal ❑ lack of time and resources ❑ lack of information on open access ❑ other[7]: ……	

15. How many new patent applications ('priority filings') have been made? *("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).*		**0**
16. Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark	**0**
	Registered design	**0**
	Other	**0**
17. How many spin-off companies were created / are planned as a direct result of the project?		**0**
Indicate the approximate number of additional jobs in these companies:		

18. Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

X	Increase in employment, or	X	In small & medium-sized enterprises
❑	Safeguard employment, or	❑	In large companies
❑	Decrease in employment,	❑	None of the above / not relevant to the project

❑	Difficult to estimate / not possible to quantify		

19. For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (*FTE = one person working fulltime for a year*) jobs:	*Indicate figure:* *30*
Difficult to estimate / not possible to quantify	❑

I Media and Communication to the general public

20. As part of the project, were any of the beneficiaries professionals in communication or media relations?

X Yes ○ No

21. As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?

X Yes ○ No

22 Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

X	Press Release	X	Coverage in specialist press
❑	Media briefing	X	Coverage in general (non-specialist) press
X	TV coverage / report	X	Coverage in national press
❑	Radio coverage / report	X	Coverage in international press
X	Brochures /posters / flyers	X	Website for the general public / internet
X	DVD /Film /Multimedia	X	Event targeting general public (festival, conference, exhibition, science café)

23 In which languages are the information products for the general public produced?

X	Language of the coordinator	X	English
X	Other language(s)		

***Question F-10*:** Classification of Scientific Disciplines according to the Frascati Manual 2002 (Proposed Standard Practice for Surveys on Research and Experimental Development, OECD 2002):

FIELDS OF SCIENCE AND TECHNOLOGY

1. NATURAL SCIENCES

1.1 Mathematics and computer sciences [mathematics and other allied fields: computer sciences and other allied subjects (software development only; hardware development should be classified in the engineering fields)]

1.2 Physical sciences (astronomy and space sciences, physics and other allied subjects)

1.3 Chemical sciences (chemistry, other allied subjects)

[6] Open Access is defined as free of charge access for anyone via Internet.

[7] For instance: classification for security project.

1.4 Earth and related environmental sciences (geology, geophysics, mineralogy, physical geography and other geosciences, meteorology and other atmospheric sciences including climatic research, oceanography, vulcanology, palaeoecology, other allied sciences)
1.5 Biological sciences (biology, botany, bacteriology, microbiology, zoology, entomology, genetics, biochemistry, biophysics, other allied sciences, excluding clinical and veterinary sciences)

2 ENGINEERING AND TECHNOLOGY
2.1 Civil engineering (architecture engineering, building science and engineering, construction engineering, municipal and structural engineering and other allied subjects)
2.2 Electrical engineering, electronics [electrical engineering, electronics, communication engineering and systems, computer engineering (hardware only) and other allied subjects]
2.3. Other engineering sciences (such as chemical, aeronautical and space, mechanical, metallurgical and materials engineering, and their specialised subdivisions; forest products; applied sciences such as geodesy, industrial chemistry, etc.; the science and technology of food production; specialised technologies of interdisciplinary fields, e.g. systems analysis, metallurgy, mining, textile technology and other applied subjects)

3. MEDICAL SCIENCES
3.1 Basic medicine (anatomy, cytology, physiology, genetics, pharmacy, pharmacology, toxicology, immunology and immunohaematology, clinical chemistry, clinical microbiology, pathology)
3.2 Clinical medicine (anaesthesiology, paediatrics, obstetrics and gynaecology, internal medicine, surgery, dentistry, neurology, psychiatry, radiology, therapeutics, otorhinolaryngology, ophthalmology)
3.3 Health sciences (public health services, social medicine, hygiene, nursing, epidemiology)

4. AGRICULTURAL SCIENCES
4.1 Agriculture, forestry, fisheries and allied sciences (agronomy, animal husbandry, fisheries, forestry, horticulture, other allied subjects)
4.2 Veterinary medicine

5. SOCIAL SCIENCES
5.1 Psychology
5.2 Economics
5.3 Educational sciences (education and training and other allied subjects)
5.4 Other social sciences [anthropology (social and cultural) and ethnology, demography, geography (human, economic and social), town and country planning, management, law, linguistics, political sciences, sociology, organisation and methods, miscellaneous social sciences and interdisciplinary , methodological and historical S1T activities relating to subjects in this group. Physical anthropology, physical geography and psychophysiology should normally be classified with the natural sciences].

6. HUMANITIES
6.1 History (history, prehistory and history, together with auxiliary historical disciplines such as archaeology, numismatics, palaeography, genealogy, etc.)
6.2 Languages and literature (ancient and modern)
6.3 Other humanities [philosophy (including the history of science and technology) arts, history of art, art criticism, painting, sculpture, musicology, dramatic art excluding artistic "research" of any kind, religion, theology, other fields and subjects pertaining to the humanities, methodological, historical and other S1T activities relating to the subjects in this group]