CLAIMS:

1. A bidirectional nucleic acid construct comprising:

a) a first segment comprising a first coding sequence for Factor IX; and

b) a second segment comprising a reverse complement of a second coding sequence for Factor IX,

wherein the construct does not comprise any of: (i) a homology arm, (ii) a promoter that drives expression of the first coding sequence for Factor IX, or (iii) a promoter that drives expression of the second coding sequence for Factor IX.

2. The bidirectional nucleic acid construct of claim 1, wherein the second coding sequence adopts a different codon usage from the first coding sequence.

3. The bidirectional nucleic acid construct of claim 1 or 2, wherein the Factor IX is wild-type Factor IX protein.

4. The bidirectional nucleic acid construct of any one of claims 1-3, wherein the bidirectional nucleic acid construct is single-stranded or double-stranded.

5. The bidirectional nucleic acid construct of any one of claims 1-4, wherein the bidirectional nucleic acid construct comprises a splice acceptor upstream of the coding sequence for Factor IX.

6. A composition comprising the bidirectional nucleic acid construct of any one of claims 1-5 for use in a method of introducing a Factor IX nucleic acid to a cell or a population of cells, wherein the method comprises delivering to the cell or cell population:

i) the bidirectional nucleic acid construct of any one of claims 1-5;

ii) an RNA-guided DNA binding agent, wherein the RNA-guided DNA binding agent is a Cas9 nuclease or a nucleic acid encoding a Cas9 nuclease; and

iii) a guide RNA (gRNA) comprising a sequence targeting a safe harbor locus.

7. The composition comprising the bidirectional nucleic acid construct for use of claim 6, wherein the safe harbor locus is the albumin locus.

8. The composition comprising the bidirectional nucleic acid construct for use of claim 7, wherein the gRNA comprises a sequence of SEQ ID NO: 40.

9. The composition comprising the bidirectional nucleic acid construct for use of claim 8, wherein the gRNA comprises the sequence of:

mU*mA*mA*AGCAUAGUGCAAUGGAUGUUUUAGAmGmCmUmAmGmAmA
mAmUmAmGmCAAGUUAAAAUAAGGCUAGUCCGUUAUCAmAmCmUmUm
GmAmAmAmAmAmGmUmGmGmCmAmCmCmGmAmGmUmCmGmGmUmGm
CmU*mU*mU*mU (SEQ ID NO: 72),

wherein "mA," "mC," "mU," and "mG" represent nucleotides that have been substituted with 2′-O-Me and * indicates a phosphorothioate (PS) bond.

10. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-9, wherein the delivering is in vitro.

11. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-10, wherein the bidirectional nucleic acid construct, the RNA-guided DNA binding agent, and/or the gRNA is administered in a nucleic acid vector and/or a lipid nanoparticle.

12. The composition comprising the bidirectional nucleic acid construct for use of claim 11, wherein the bidirectional nucleic acid construct, the RNA-guided DNA binding agent and/or the gRNA is administered in a viral vector.

13. The composition comprising the bidirectional nucleic acid construct for use of claim 12, wherein the viral vector is an adeno associated viral (AAV) vector.

14. The composition comprising the bidirectional nucleic acid construct for use of claim 13, wherein the AAV vector is selected from the group consisting of AAV1, AAV3, AAV4, AAV5, AAV6, AAV8, AAV-DJ, and AAV2/8.

15. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-14, wherein the RNA-guided DNA binding agent is the Cas9 nuclease.

16. The composition comprising the bidirectional nucleic acid construct for use of any one

of claims 6-14, wherein the RNA-guided DNA binding agent is an mRNA encoding the Cas9 nuclease.

17. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-16, wherein the Cas9 nuclease is an *S. pyogenes* Cas9 nuclease.

18. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-17, wherein the bidirectional nucleic acid construct, RNA-guided DNA binding agent, and gRNA are administered sequentially or simultaneously, in any order and/or in any combination.

19. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-18, wherein the RNA-guided DNA binding agent has site-specific DNA binding activity.

20. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-19, wherein the cell or population of cells, to which the Factor IX nucleic acid has been introduced, expresses Factor IX with a heterologous signal peptide.

21. The composition comprising the bidirectional nucleic acid construct for use of claim 20, wherein the cell or population of cells, to which the Factor IX nucleic acid has been introduced, expresses Factor IX with an albumin signal peptide.

22. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-19, wherein the cell or population of cells, to which the Factor IX nucleic acid has been introduced, expresses Factor IX with a Factor IX signal peptide.

23. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-22, wherein the cell or population of cells is or includes a liver cell or a population of liver cells.

24. The composition comprising the bidirectional nucleic acid construct for use of claim 23, wherein the liver cell or the population of liver cells is a hepatocyte or a population of hepatocytes.

25. The composition comprising the bidirectional nucleic acid construct for use of any one of claims 6-24, wherein the bidirectional nucleic acid construct, RNA-guided DNA binding agent, and gRNA, in any combination, are administered within an hour of each other.

26. The composition comprising the bidirectional nucleic acid construct of any one of claims 1-5 for use in a method of treating a Factor IX deficiency, wherein the method comprises administering to an individual with the Factor IX deficiency:

i) the bidirectional nucleic acid construct;

ii) a Cas9 nuclease or a nucleic acid encoding a Cas9 nuclease; and

iii) a guide RNA (gRNA) comprising a sequence targeting a safe harbor locus.

27. The composition comprising the bidirectional nucleic acid construct for use according to claim 26, wherein the treatment comprises expressing a therapeutically effective amount of the Factor IX protein.

28. The composition comprising the bidirectional nucleic acid construct for use according to claim 26 or 27, wherein the treatment comprises achieving a therapeutically effective level of circulating Factor IX coagulation activity in the individual.

29. The composition comprising the bidirectional nucleic acid construct for use according to any one of claims 26-28, wherein the individual is a human.

30. The composition comprising the bidirectional nucleic acid construct for use according to claim 29, wherein the treatment further comprises achieving circulating Factor IX activity or human Factor IX protein levels of at least about 1% of normal.

31. The composition comprising the bidirectional nucleic acid construct for use according to claim 29 or 30, wherein the circulating Factor IX activity or human Factor IX protein levels is less than about 150% of normal.

32. The composition comprising the bidirectional nucleic acid construct for use according to claims 29 or 30, wherein the treatment further comprises achieving circulating Factor IX activity or human Factor IX protein levels of at least about 1% to about 150% of normal.

33. The composition comprising the bidirectional nucleic acid construct for use according to any one of claims 29 to 32, wherein the treatment further comprises achieving an increase in Factor IX activity over the individual's baseline Factor IX activity of at least about 1% of normal Factor IX activity.

34. The composition comprising the bidirectional nucleic acid construct for use according to any one of claims 29 to 33, wherein the treatment further comprises achieving an increase in Factor IX activity over the individual's baseline Factor IX activity of at least about 50% of normal Factor IX activity.

35. A vector comprising the bidirectional nucleic acid construct of any one of claims 1-5.

36. The vector of claim 35, wherein the vector is a viral vector.

37. A lipid nanoparticle comprising the bidirectional nucleic acid construct of any one of claims 1-5.

38. A cell comprising the bidirectional nucleic acid construct of any one of claims 1-5.

39. The bidirectional nucleic acid construct of any one of claims 1-5, for use in a method of introducing a Factor IX nucleic acid to a cell or a population of cells.

40. A composition comprising the bidirectional nucleic acid construct of any one of claims 1-5, for use in a method of treating a Factor IX deficiency.

41. A kit or composition for use in a method of introducing a Factor IX nucleic acid to a cell or a population of cells comprising:

i) the bidirectional nucleic acid construct of any one of claims 1-5;

ii) a Cas9 nuclease or a nucleic acid encoding a Cas9 nuclease; and

iii) a guide RNA (gRNA) comprising a sequence targeting a safe harbor locus.

42. An *in vitro* method of introducing a Factor IX nucleic acid to a cell or a population of

cells, wherein the method comprises delivering to the cell or cell population:

i) the bidirectional nucleic acid construct, the vector, or the lipid nanoparticle of any one of claims 1-5 and 35-37;

ii) an RNA-guided DNA binding agent, wherein the RNA-guided DNA binding agent is a Cas9 nuclease or a nucleic acid encoding a Cas9 nuclease; and

iii) a guide RNA (gRNA) comprising a sequence targeting a safe harbor locus.

43. The bidirectional nucleic acid construct, the vector, or the lipid nanoparticle of any one of claims 1-5 and 35-37, for use in therapy.

44. Use of the bidirectional nucleic acid construct, the vector, or the lipid nanoparticle of any one of claims 1-5 and 35-37, in the manufacture of a medicament for treating a Factor IX deficiency.

45. The use of claim 44, wherein the Factor IX deficiency is hemophilia or hemophilia B.